CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2022-2023

"Biais liés au sexe dans la susceptibilité aux maladies: causes génétiques et épigénétiques"

Cours I - Introduction : les maladies ont-elles un sexe ? *6 mars*

Cours II - Biais liés au sexe : comment distinguer les effets dus aux chromosomes sexuels, hormones ou mode de vie ? *13 mars*

Cours III - L'impact de l'expression des gènes liés aux chromosomes X inactif et Y sur les différences entre les sexes. *20 mars*

Cours IV - L'importance de la régulation du dosage des gènes sur le chromosome X dans la susceptibilité à certaines maladies. *27 mars*

Colloque – en lien avec le sujet du cours, le **21 avril, 2023**

CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Image : *La chute de l'homme* (détail), Cornelis Cornelisz van Haarlem, 1592. © Rijksmuseum

COLLOQUE

The Genetic and Epigenetic Basis of Sex Bias in Disease

21 avril 2023

COLLÈGE DE FRANCE 1530

Thomas Römer
Administrateur du Collège de France
11, place Marcelin-Berthelot, 75005 Paris
www.college-de-france.fr

Année académique 2022/2023

21 avril 2023 de 9h à 18h
Amphitheatre Maurice Halbwachs

The Genetic and Epigenetic Basis of Sex Bias in Disease

Edith Heard, Chaire Épigénétique & mémoire cellulaire
Scientific co-organisers: **James Cleland** and **Agnese Loda**

Daniel Andergassen
Technical University of Munich, Germany

Richard Festenstein
Imperial College, London, UK

Cornelius Gross
EMBL-Rome, Italy

Jean-Charles Guéry
INSERM, University of Toulouse, France

Jamie Hackett
EMBL-Rome, Italy

Irene Miguel-Aliaga
Imperial College, London, UK

Jessica Tollkuhn
Cold Spring Harbor Lab, New York, USA

Taru Tukiainen
FIMM, Helsinki, Finland

Judith Zaugg
EMBL Heidelberg, Germany

Colloquium in English, free entry, no registration required

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E. Heard, March 6th 2023

CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2022-2023

"Biais liés au sexe dans la susceptibilité aux maladies: causes génétiques et épigénétiques"

6 mars, 2023

Cours I

Introduction : les maladies ont-elles un sexe ?

Exploring the origins of sex bias in human disease:

La chute de l'homme
Cornelis Cornelisz van Haarlem, 1592
(Rijksmuseum d'Amsterdam)

Female and male health throughout history (very brief overview)

What is biological sex?

How is it genetically and/or environmentally established?

Sexual dimorphism and the many levels we understand today

Considerations about gender and biological sex

Implications for human health

E. Heard, March 6th 2023

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Diseases of Women in Ancient History

The wondering womb…

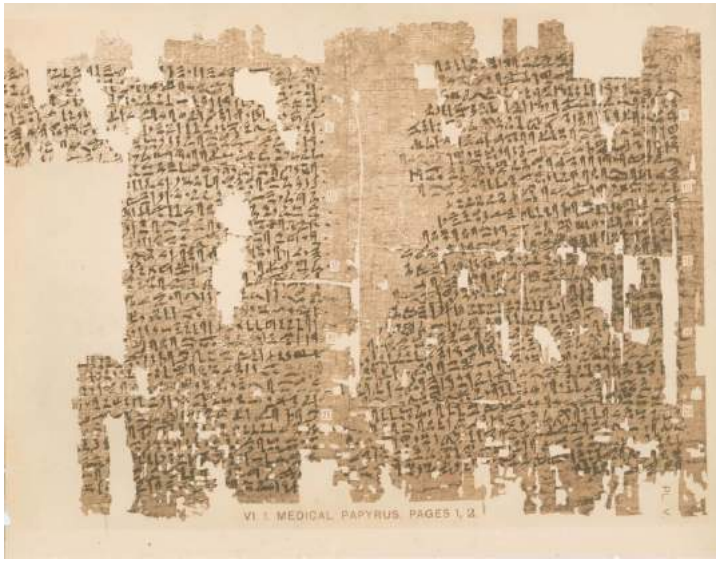
From ancient Egypt and Greece, the ailments of women were almost always attributed to the uterus

The **Kahun Gynaecological Papyrus** (**Petrie Medical Papyrus**, **Kahun Medical Papyrus**, **Lahun Medical Papyrus**, or **UC32057**) is the oldest known medical text in Egypt

Examination of a woman whose eyes are aching till she cannot see, on top of aches in her neck:
You should say of it 'it is discharges of the womb in her eyes'.
You should treat it by fumigating her with incense and fresh oil, fumigating her womb with it, and fumigating her eyes with goose leg fat.
You should have her eat a fresh ass liver

Examination of a woman who is ill from her womb wandering
You should say of it 'what do you smell?'
If she tells you 'I smell roasting'
You should say of it 'it is wrappings (?) of the womb'
You should treat it by fumigating her with whatever she smells as roast'

Examination of a woman aching in her molars, her front, and her ears so much that she hears no word
You should say of it 'it is terrors of the womb'.
You should treat it with the same prescription used for removing detritus of the womb



www.ucl.ac.uk/museums-static/digitalegypt/med/birthpapyrus.html

Dated circa 1800 BCE
Found at El-Lahun (Faiyum, Egypt)
Currently in Museum of University College London, UK

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Diseases of Women in Ancient History

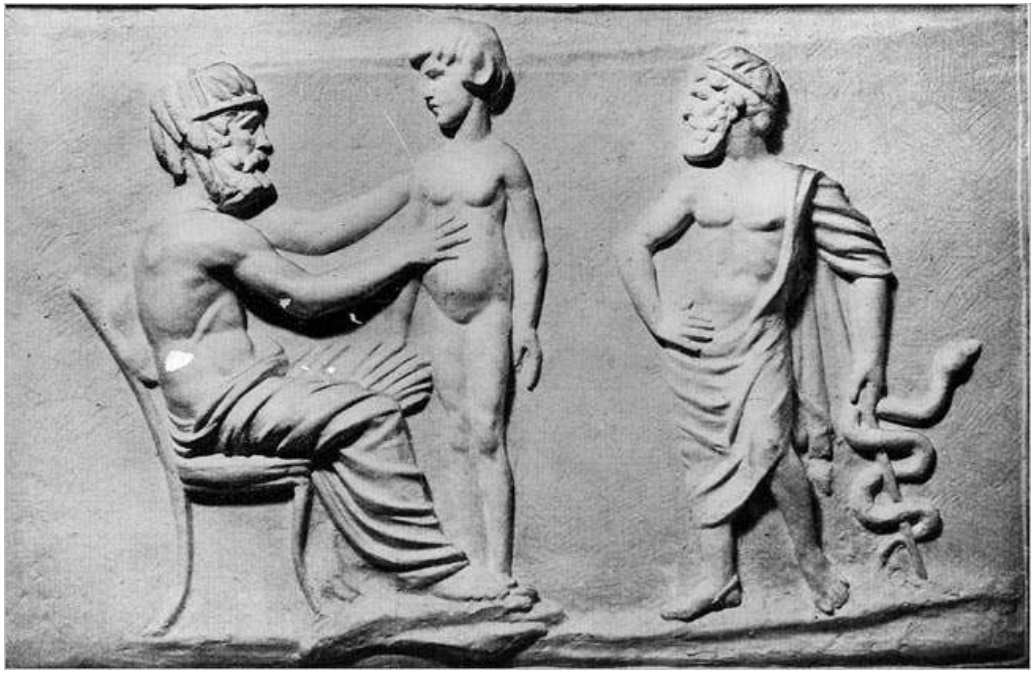
The wondering womb…

For the ancient Greeks, the womb was the source of all ailments

Aristotle held that a woman was a “deformed” or “mutilated” male “

Plato in the Timaeus, defined the female uterus as “an animal eager to procreate.” “If it remains without producing fruit for a long time,” added the philosopher, “it becomes irritated and angry; it wanders throughout the body, closes the passage to the air, prevents breathing, puts the body in extreme danger, and engenders a thousand diseases.”

Hippocrates (460-377 BC) taught that the womb wandered around in a woman's body, causing disease as a consequence of its impact on other tissues.



Hulton Archive/Getty Images

The Wandering Womb: A Cultural History of Outrageous Beliefs About Women
Lana Thompson 1999

E. Heard, March 6th 2023

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Diseases of Women in History

The wondering womb

The Greek physician Galen wrote that "the man is more perfect than the woman, [who is] less perfect than the man in respect to the generative parts." He proposed that the uterus was an interior scrotum

He noted that while the womb may seem to be moving, it's actually the tension of the membranes that hold it in place that pull it up slightly. The problem, he claimed, was the "suffocation" of the womb by a build up of menstrual blood or, even worse, the female version of "seed" that mixed with male sperm. Retained seed would proceed to rot and produce vapors that corrupt the other organs.

For the single woman suffering from hysteria, the cure was simple: marriage, followed by children.

Physicians prescribed all kinds of treatments for a wayward womb. Eg sweet-smelling vaginal suppositories and fumigations to tempt the uterus back to its rightful place. The Greek physician Atreaus wrote that the womb "delights…in fragrant smells and advances towards them; and it has an aversion to foetid smells, and flees from them." Women were also advised to ingest disgusting substances—sometimes containing repulsive ingredients such as human or animal excrement—in order to coax the womb away from the lungs and heart.
In some cases, physical force was used to correct the position of a wandering womb.

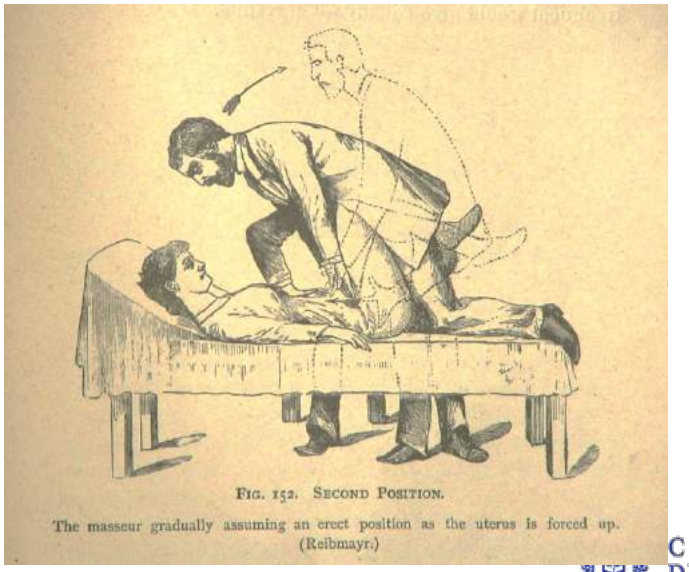

FIG. 152. SECOND POSITION.

The masseur gradually assuming an erect position as the uterus is forced up. (Reibmayr.)

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Diseases of Women in History

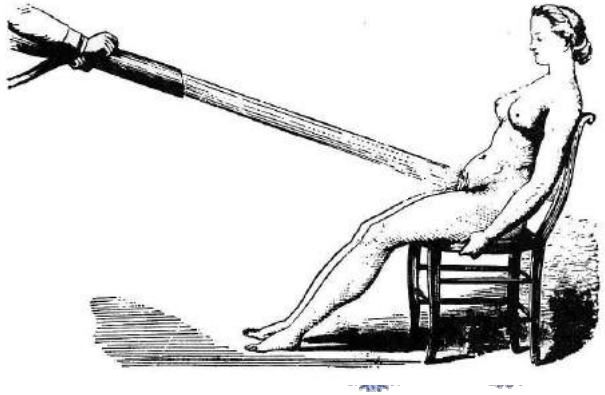
The womb as the cause of psychological dysfunction

Medieval medical practitioners believed the uterus to be a distinctly female organ that caused a host of specifically female diseases.

"The uterus is called also *matrix* because it is the mother of all," wrote John Moir in 1620.

In the 1700s, the theorized cause of hysteria began to shift from the womb to the brain. they were very much to blame for the ostensible irrationality of women. Over the course of several thousand years, the womb had become less and less of a way to explain physical ailments, and more and more of a way to explain psychological dysfunction.

Even through to the 19th century, countless cures for haywire wombs were peddled including hypnosis, blasting a woman's abdomen with jets of water...



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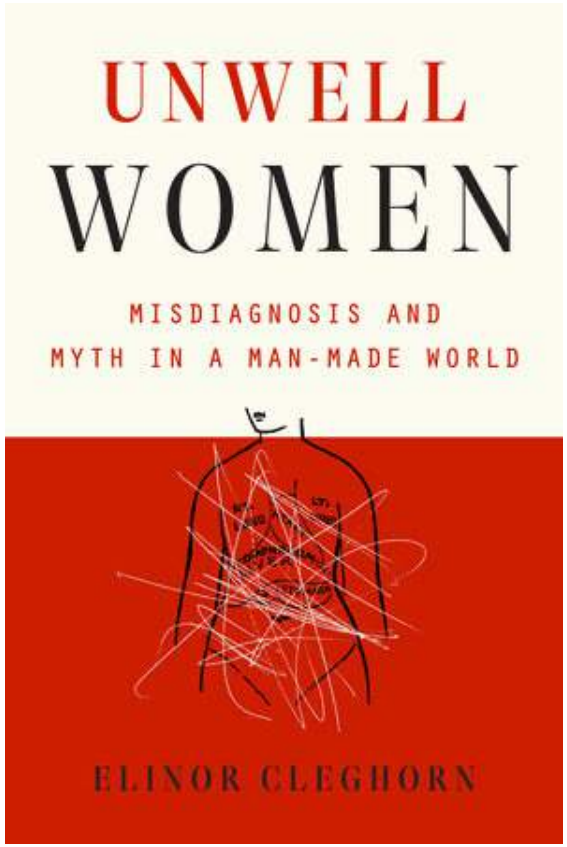
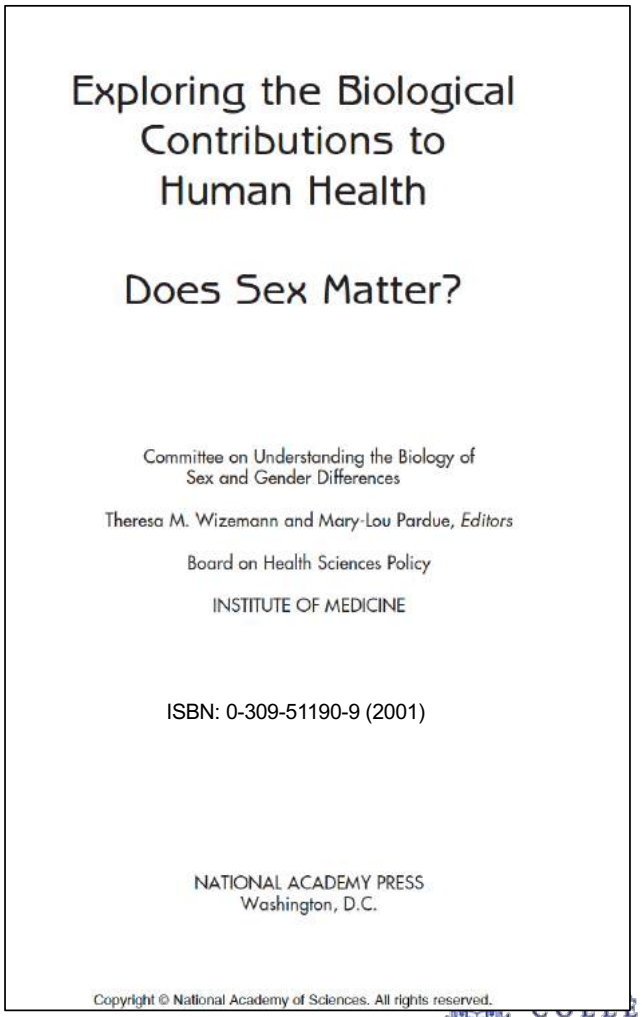
Diseases of Women from Ancient History to Modern times



The Wandering Womb: A Cultural History of Outrageous Beliefs About Women, Lana Thompson 1999


Exploring the Biological Contributions to Human Health

Does Sex Matter?

Committee on Understanding the Biology of Sex and Gender Differences

Theresa M. Wizemann and Mary-Lou Pardue, *Editors*

Board on Health Sciences Policy

INSTITUTE OF MEDICINE

ISBN: 0-309-51190-9 (2001)

NATIONAL ACADEMY PRESS
Washington, D.C.

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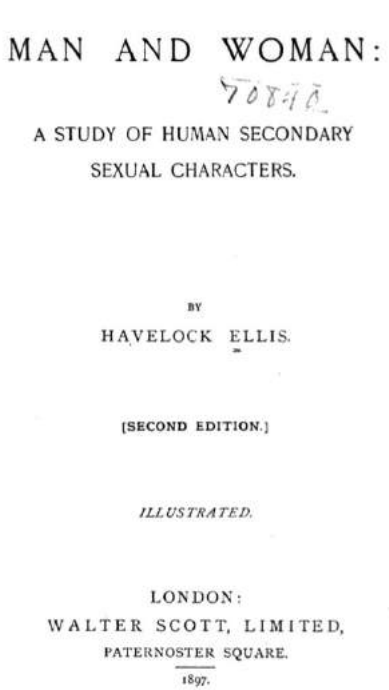
E. Heard, March 6th 2023

Man and Woman : a Study of Human Secondary Sexual Characters



MAN AND WOMAN:

A STUDY OF HUMAN SECONDARY SEXUAL CHARACTERS.

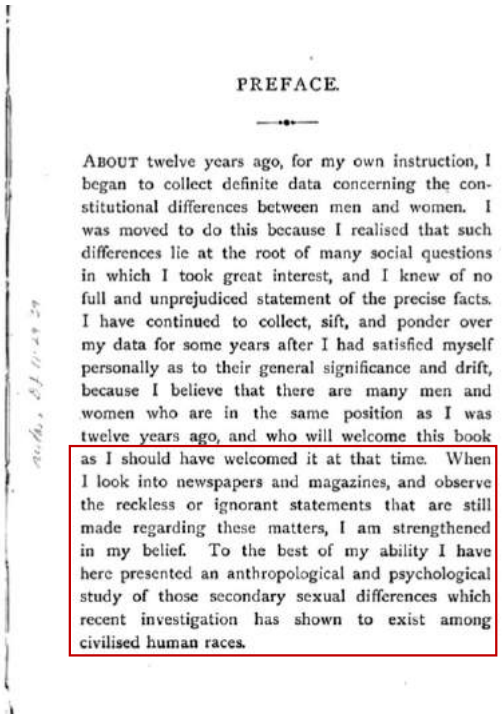
BY

HAVELOCK ELLIS.

[SECOND EDITION.]

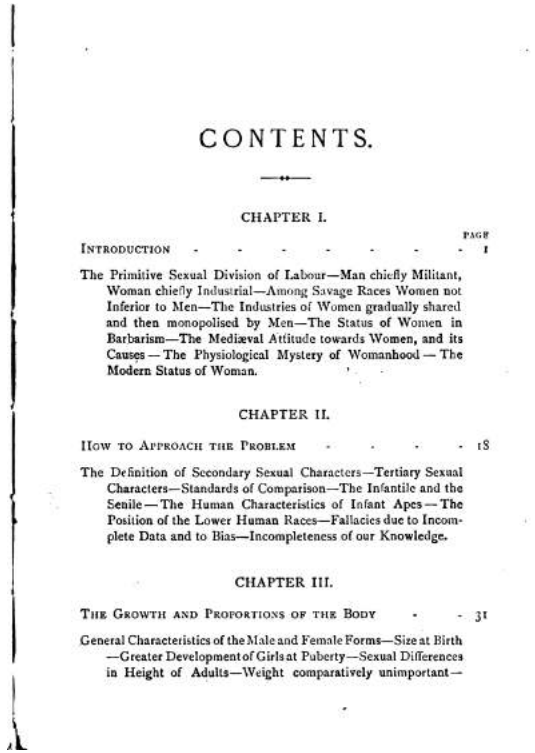
ILLUSTRATED.

LONDON:
WALTER SCOTT, LIMITED,
PATERNOSTER SQUARE.
1897.



PREFACE.

ABOUT twelve years ago, for my own instruction, I began to collect definite data concerning the constitutional differences between men and women. I was moved to do this because I realised that such differences lie at the root of many social questions in which I took great interest, and I knew of no full and unprejudiced statement of the precise facts. I have continued to collect, sift, and ponder over my data for some years after I had satisfied myself personally as to their general significance and drift, because I believe that there are many men and women who are in the same position as I was twelve years ago, and who will welcome this book as I should have welcomed it at that time. When I look into newspapers and magazines, and observe the reckless or ignorant statements that are still made regarding these matters, I am strengthened in my belief. To the best of my ability I have here presented an anthropological and psychological study of those secondary sexual differences which recent investigation has shown to exist among civilised human races.



CONTENTS.

Ellis H. “Man and woman: a study of human secondary sexual characters” vol. 24. London: Walter Scott; 1911.

E. Heard, March 6th 2023

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What is Biological Sex?

Biological sex, strictly defined means the “gametic” sex and not secondary sexual characteristics, although the definition has drifted in recent years

Many species including humans have two, distinct biological sexes, distinguished by the way that they package their DNA into ‘gametes’ : the sex cells that merge to make a new organism.

Males produce small mobile gametes, females produce large and generally immobile gametes.

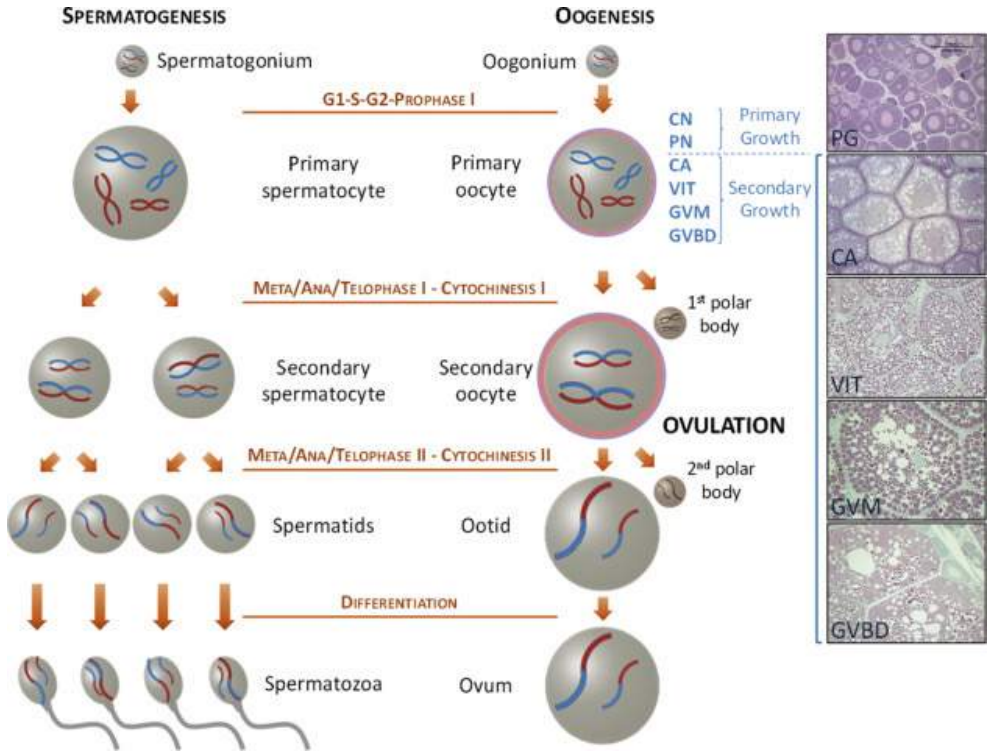
Male and female gametes are very different in structure, as well as in size (human sperm and eggs, worms, flies, fish, molluscs, trees, grasses etc)

Different species manifest the two sexes in different ways

Different species determine sex in different ways

1862 ‘We do not even in the least know the final cause of sexuality; why new beings should be produced by the union of the two sexual elements, instead of by a process of parthenogenesis . . . The whole subject is as yet hidden in darkness’.

– C. R. Darwin
J. Proc. Linn. Soc. (Botany) 6, 77-96



Anisogamy, or the size differences of gametes (sex cells), is in fact the defining feature of the two sexes.

According to evolutionary biologist, Michael Majerus there is no other universal difference between males and females

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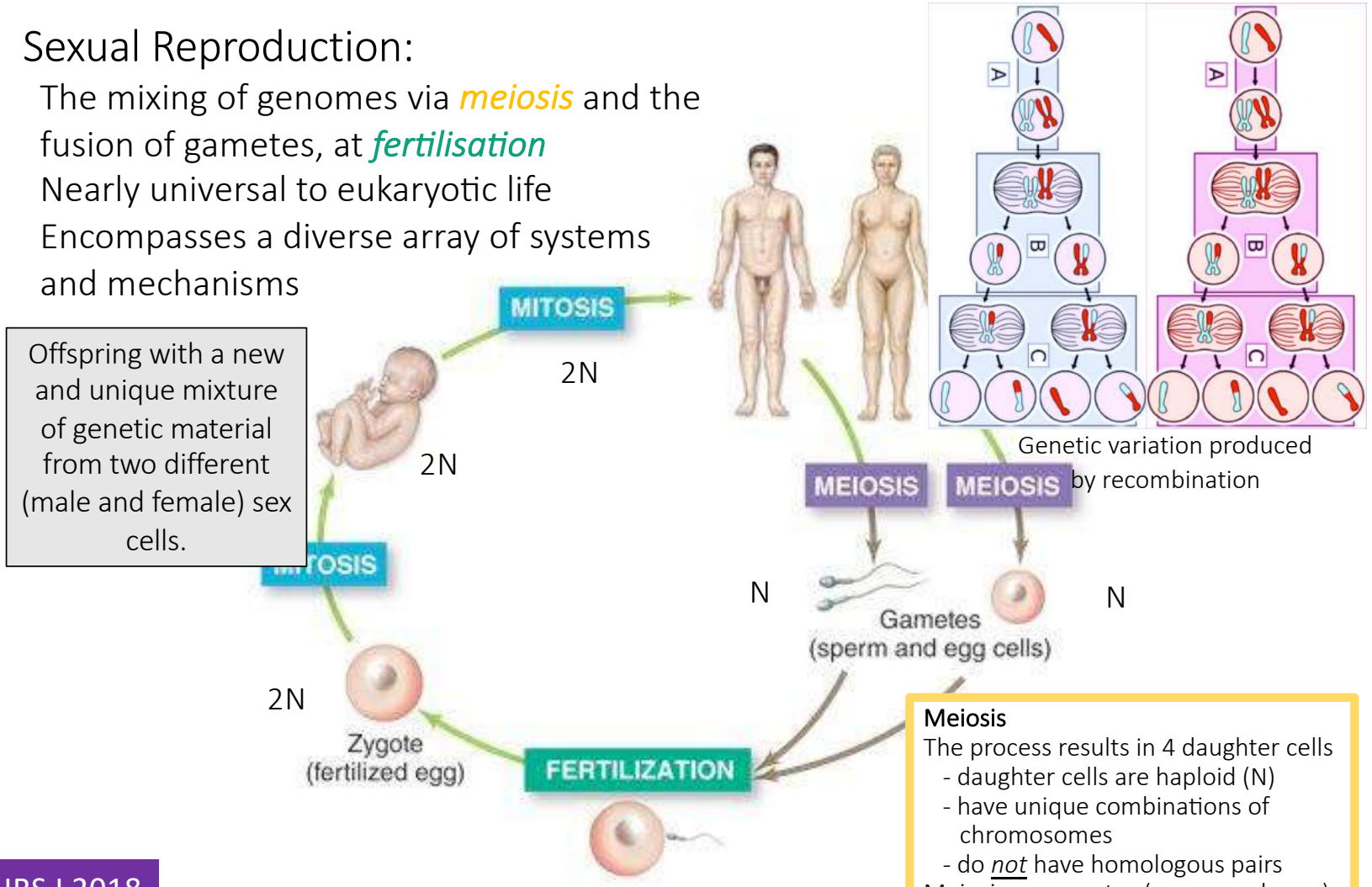
Sexual Reproduction and Anisogamy (in humans)

Sexual Reproduction:

- The mixing of genomes via *meiosis* and the fusion of gametes, at *fertilisation*
- Nearly universal to eukaryotic life
- Encompasses a diverse array of systems and mechanisms



Offspring with a new and unique mixture of genetic material from two different (male and female) sex cells.

Genetic variation produced by recombination

Meiosis
The process results in 4 daughter cells
- daughter cells are haploid (N)
- have unique combinations of chromosomes
- do *not* have homologous pairs

Meiosis => gametes (sperm and eggs)

Voir COURS I 2018

Sex Determination

Multiple Strategies: genetic and non-genetic

Non-genetic (ie no DNA sequence difference between the sexes)
can be environmental, temperature-dependent, epigenetic…

Genetic
Sex determining locus or loci – can lead to evolution of sex chromosomes

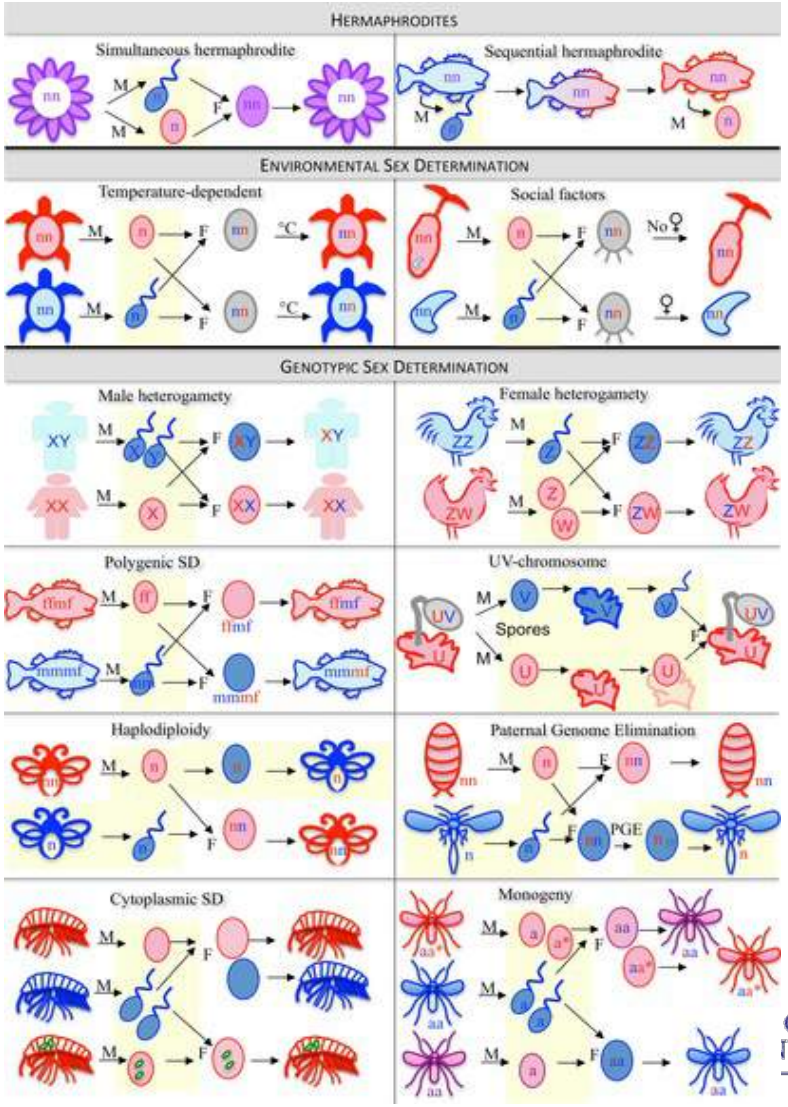
Mixed: genetic and non-genetic or even epigenetic
Sex chromosomes and environmental sex determination
Eg many fish, plants…

Males and females can exist in the same organism (hermaphrodites eg plants, worms and many others) or as separate organisms (eg mammals)
While the evolution of anisogamy led to the evolution of male and female functions, the evolution of separate sexes is *not* inevitable across lineages.

There are many ways to evolve sex determination

Voir COURS I 2018

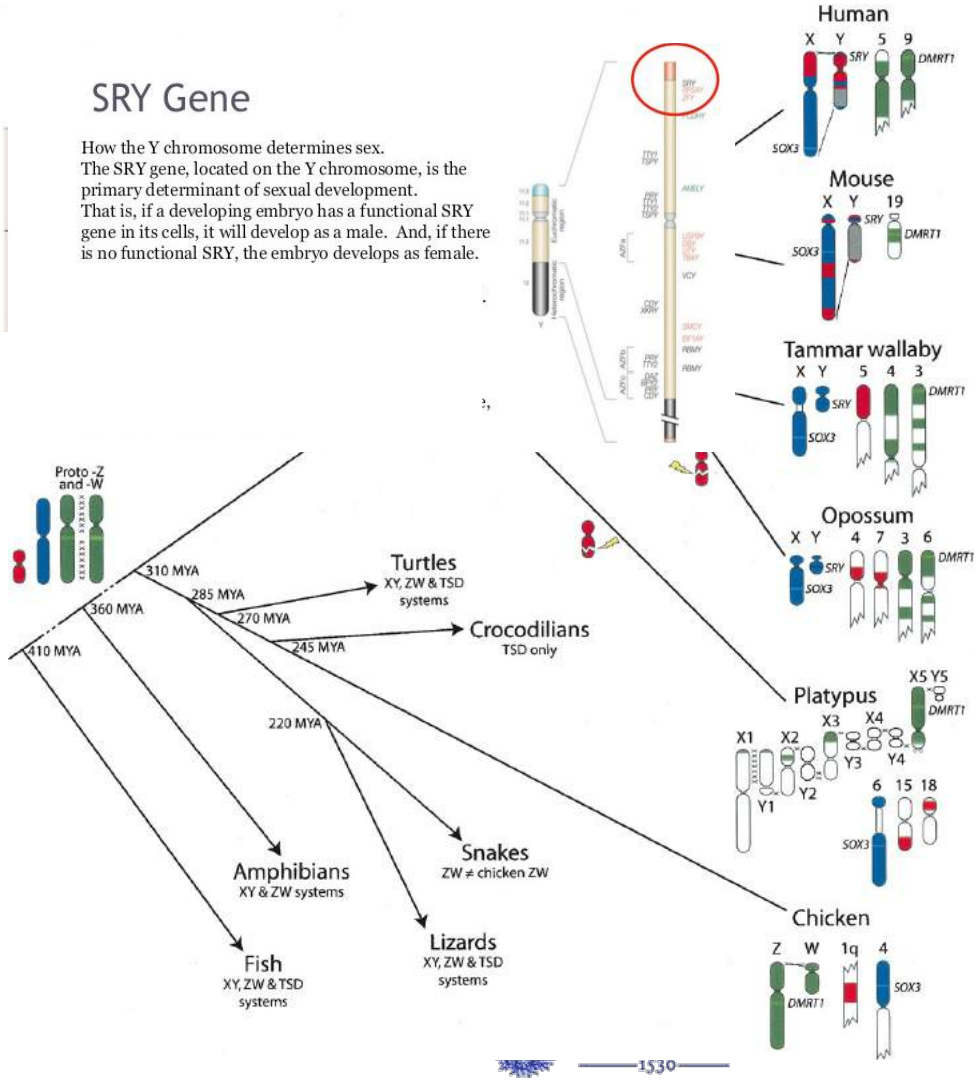
- Sexual reproduction is an ancient feature of life on earth
- Sex determination of males and females occurs via a diversity of mechanisms, evolving rapidly
- However - diversity in primary sex-determining signals is coupled with conserved molecular pathways that trigger male or female development.



Bachtrog lab, Plos Genet 2014

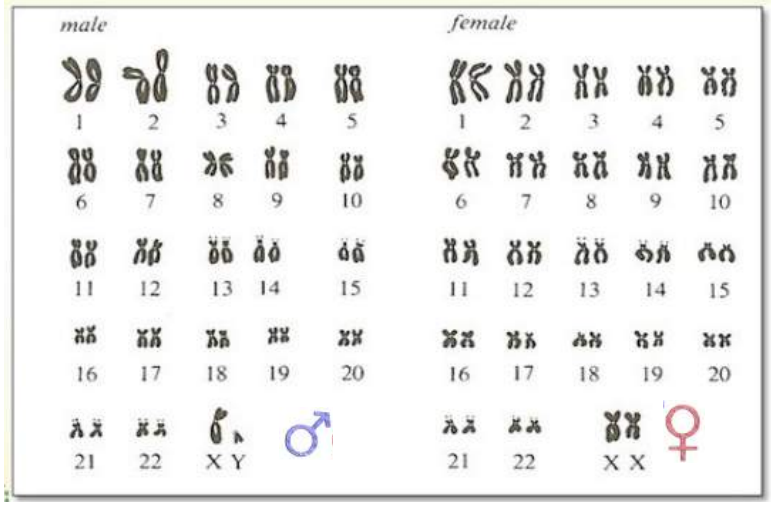
Human Sex Determination

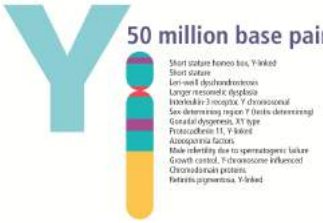
- In humans, sex is determined by the sex chromosomes (XX females, XY males).
- They originated from a set of autosomes during the early evolution of mammals.
- Restriction of recombination followed by gene loss on the Y resulted in the morphological differentiation of sex chromosomes (COURS 2018)
- The vast majority of genes on the sex chromosomes are not directly involved in sex determination, and development as a (gametic) male or female depends on the presence/absence of a master sex-determining locus, the *Sry* gene, on the male-limited Y chromosome.
- Expression of *Sry* early in embryonic development initiates testis differentiation by activating male-specific developmental networks, while in its absence, ovaries develop.
- The first visible signs of sexual differentiation of the ovary and testis occur by the sixth week of gestation in humans and sex hormones initiate further sexual differentiation in nongonadal tissues and organs. When this developmental process is disrupted, this can lead to ambiguous external genitalia (upto one in 4,500 infants) to sterility (which is more cryptic and difficult to diagnose but more common). See COURS II 2023



E. Heard, March 6th 2023

Human Sex Chromosomes





X: >1000 genes

Y: ~100 genes

Sry (testis determinant factor)

Eif2s3y (spermatogenesis)

- Humans normally have 46 chromosomes: 23 pairs, one set from each parent
- Plus 1 pair of sex chromosomes, **the X and the Y** or **the inactive X and the active X**
- The other chromosomes are numbered 1-22
- A person with 2 X chromosomes (46, XX) is considered female
- A person with an X and a Y (46, XY) is considered male
- The sex chromosomes lead to dramatic differences in gene content and expression
- To accommodate this imbalance, dosage compensation mechanisms have evolved
- X-chromosome inactivation is the process that leads to silencing of almost all genes on one X in individuals with more than one X
- Sex chromosomes evolve as a consequence of sexual reproduction (enabling sex determination and gonad differentiation) COURS 2018
- However their genes also influences non-gonadal tissues with implications for diseases COURS 2023

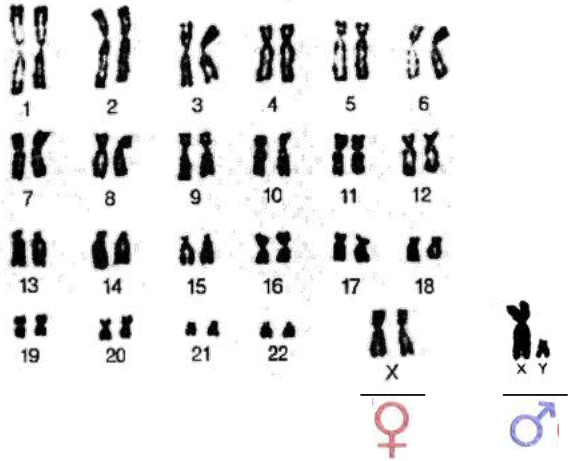
Mammalian X-chromosome inactivation

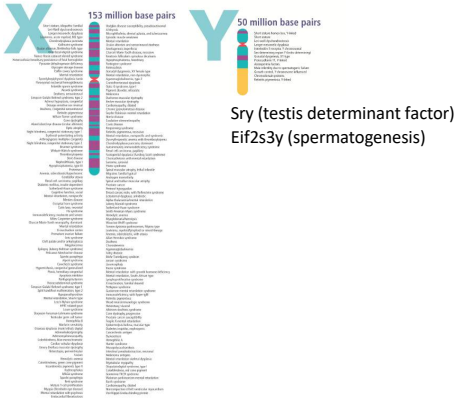
COURS III/IV 2023

Essential process of sex chromosome dosage compensation and a paradigm of epigenetics

Differential expression of almost all genes on one of the two X chromosomes in females

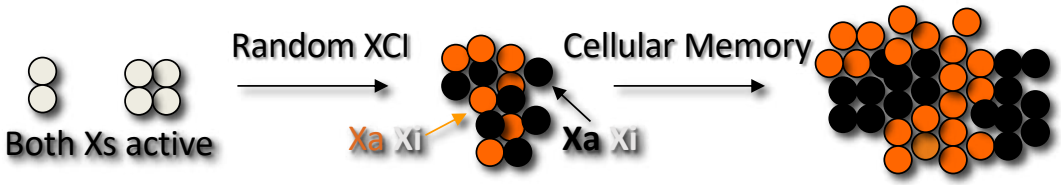
A significant no.of genes on the Xi can escape silencing, leading to variations in protein dosage



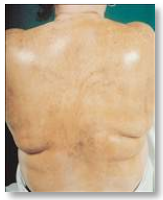


Sry (testis determinant factor)
Eif2s3y (spermatogenesis)

Mary Lyon
(1929-2014)



Phenotypic variation within the same individual…



Females are mosaics for X-linked traits

Lyon, M. F. (1961), Gene Action in the X-chromosome of the Mouse (Mus musculus) L. *Nature* 190: 372-3.

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Escape from XCI in females: an added layer of cellular mosaicism in X-linked gene expression

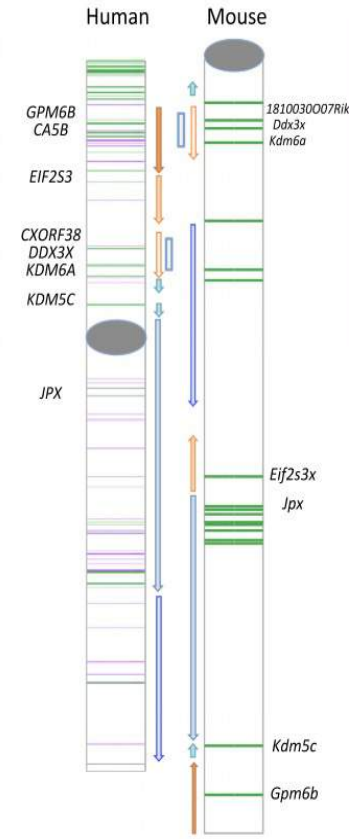
COURS III/IV 2023

In humans, up to 25% of X-linked genes can escape from X inactivation!

10% of these escape constitutively
15% of these genes show variability between individuals – and tissue specificity

X-inactivation profile reveals extensive variability in X-linked gene expression in females

Carrel and Willard (2005) *Nature* 434, 400-404



- Escape may underlie sex chromosome dosage effects in several sex-biased diseases (metabolic, immune and neurological phenotypes, cancer)
- Some escapees are clearly implicated in triggering these disease
- Some escapees provide therapeutic potential (eg *Mecp2* in Rett's syndrome)

Balaton et al., *Trends in Genetics* 2016.

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Human Sex Determination

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E. Heard, March 6th 2023

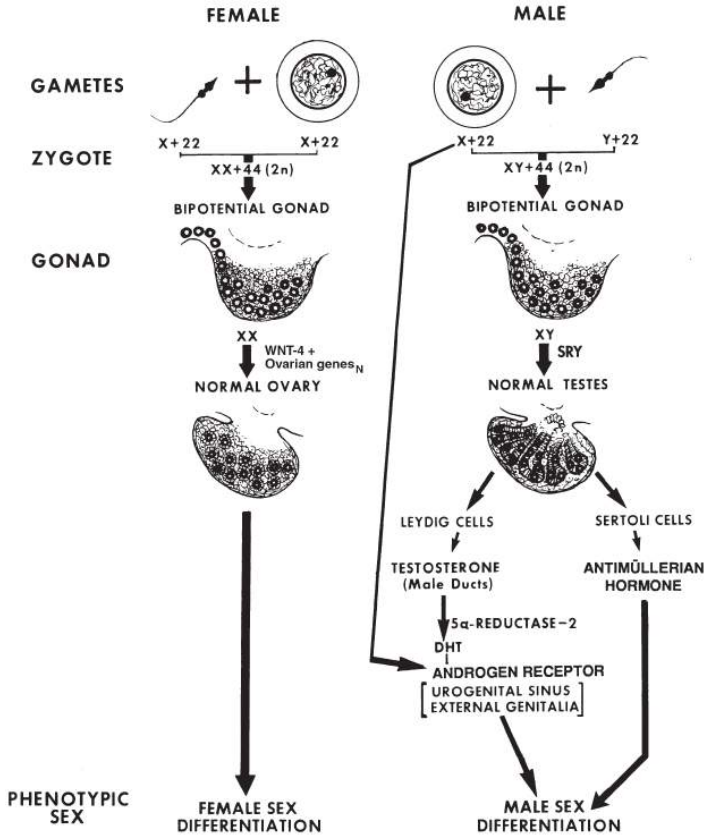
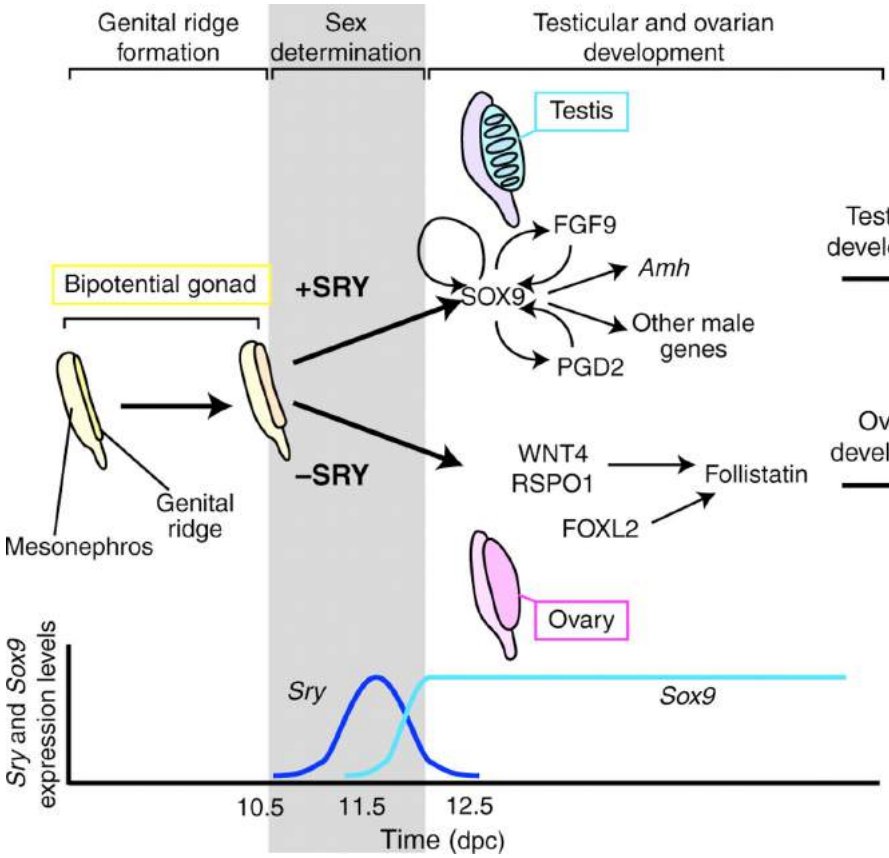
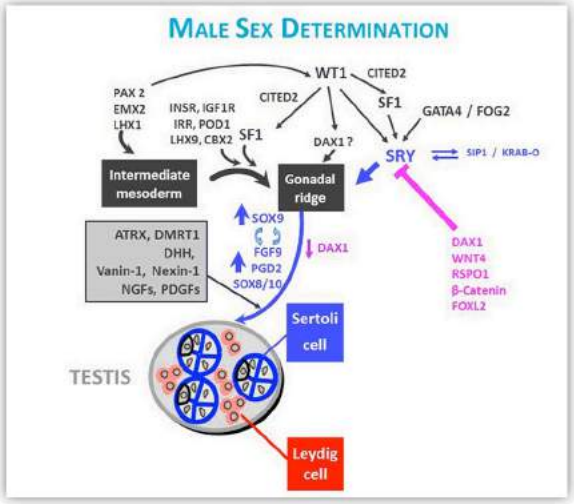
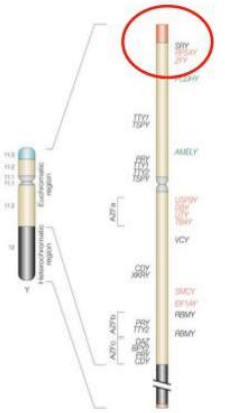


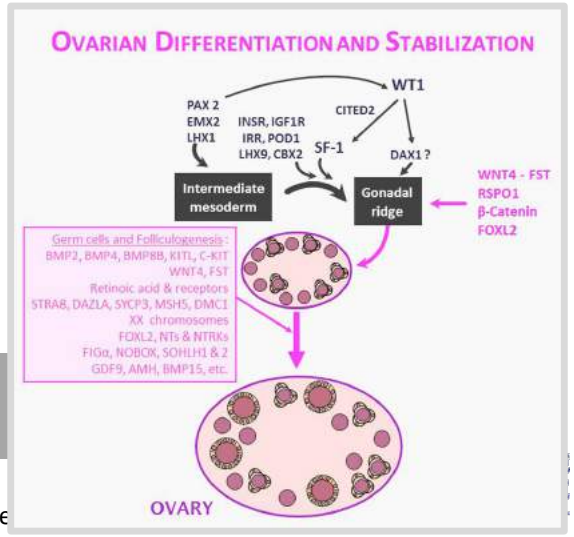
FIGURE 3-1 From genotype to phenotype: a diagrammatic representation of human sex determination and differentiation. Intrinsic or extrinsic factors adversely affecting any stage of these processes can lead to anomalies of sex. Source: Grumbach and Conte (1998, Figure 29-28, p. 1329). Reprinted, with permission, from M. M. Grumbach and F. A. Conte. 1998. *In: Williams Textbook of Endocrinology*, 9th ed. J. D. Wilson, D. W. Foster, H. M. Kronenberg, and P. R. Larsen, eds. Philadelphia: W. B. Saunders Co. Copyright by W. B. Saunders Company, Philadelphia.

Primary Sex Determination









NB It is not the primordial germ cells which respond to SRY presence or absence, but the **supporting cells** within the developing gonad.

Kenichi Kashimada, Peter Koopman
Development 2010 137: 3921-3930; doi: 10.1242/de

Primary Sex Determination mapped at the single cell level

Article

Single-cell roadmap of human gonadal development

https://doi.org/10.1038/s41586-022-04918-4
Received: 5 May 2021
Accepted: 30 May 2022
Published online: 6 July 2022

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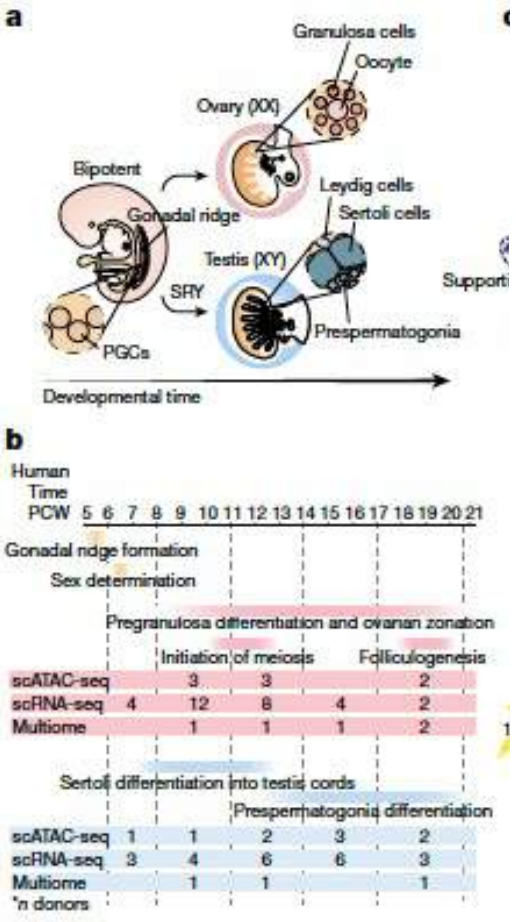
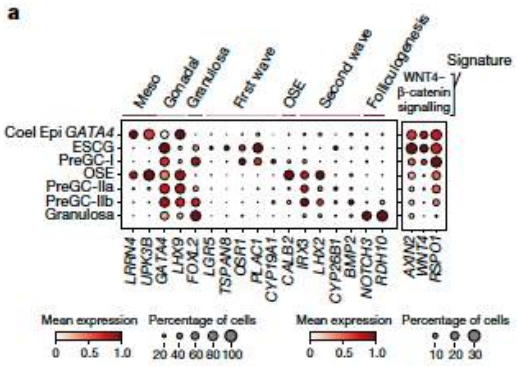
Gonadal development is a complex process that involves sex determination followed by divergent maturation into either testes or ovaries[1]. Historically, limited tissue accessibility, a lack of reliable in vitro models and critical differences between humans and mice have hampered our knowledge of human gonadogenesis, despite its importance in gonadal conditions and infertility. Here, we generated a comprehensive map of first- and second-trimester human gonads using a combination of single-cell and spatial transcriptomics, chromatin accessibility assays and fluorescent microscopy. We extracted human-specific regulatory programmes that control the development of germline and somatic cell lineages by profiling equivalent developmental stages in mice. In both species, we define the somatic cell states present at the time of sex specification, including the bipotent early supporting population that, in males, upregulates the testis-determining factor *SRY* and sPAX8s, a gonadal lineage located at the gonadal–mesonephric interface. In females, we resolve the cellular and molecular events that give rise to the first and second waves of granulosa cells that compartmentalize the developing ovary to modulate germ cell differentiation. In males, we identify human *SIGLEC15*$^+$ and *TREM2*$^+$ fetal testicular macrophages, which signal to somatic cells outside and inside the developing testis cords, respectively. This study provides a comprehensive spatiotemporal map of human and mouse gonadal differentiation, which can guide in vitro gonadogenesis.



Human–mouse harmonized single-cell atlases of gonadal and extragonadal tissue



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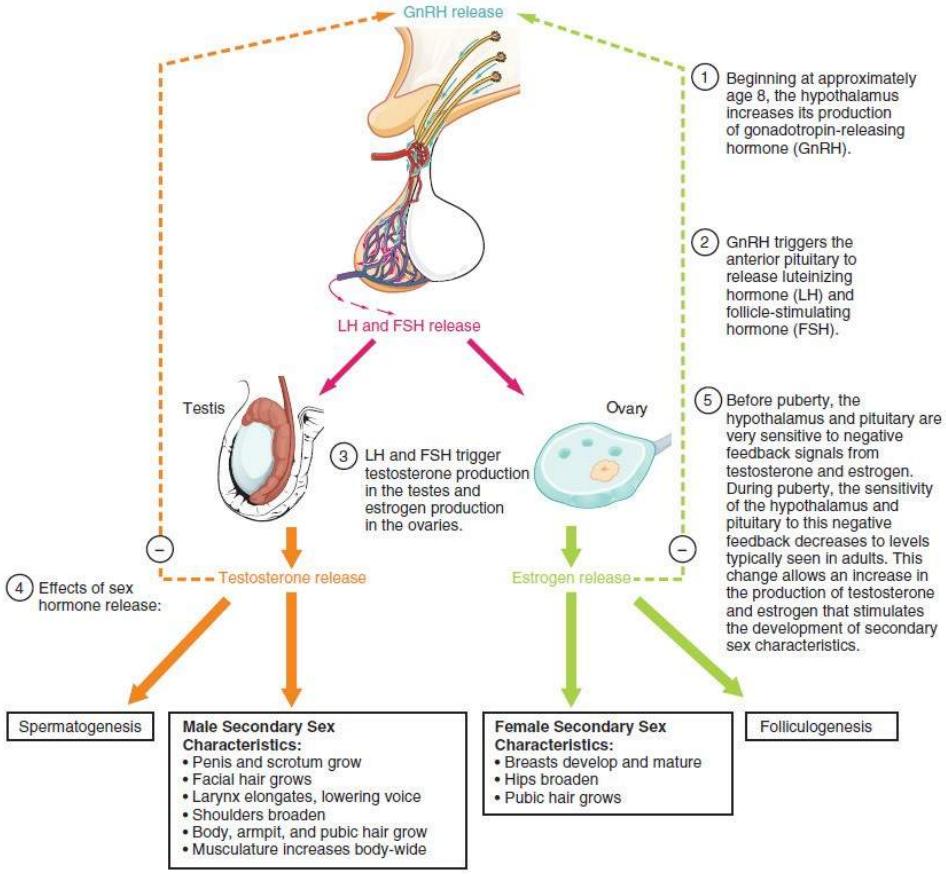
Human Sex Determination

Three levels of Sexual Development:

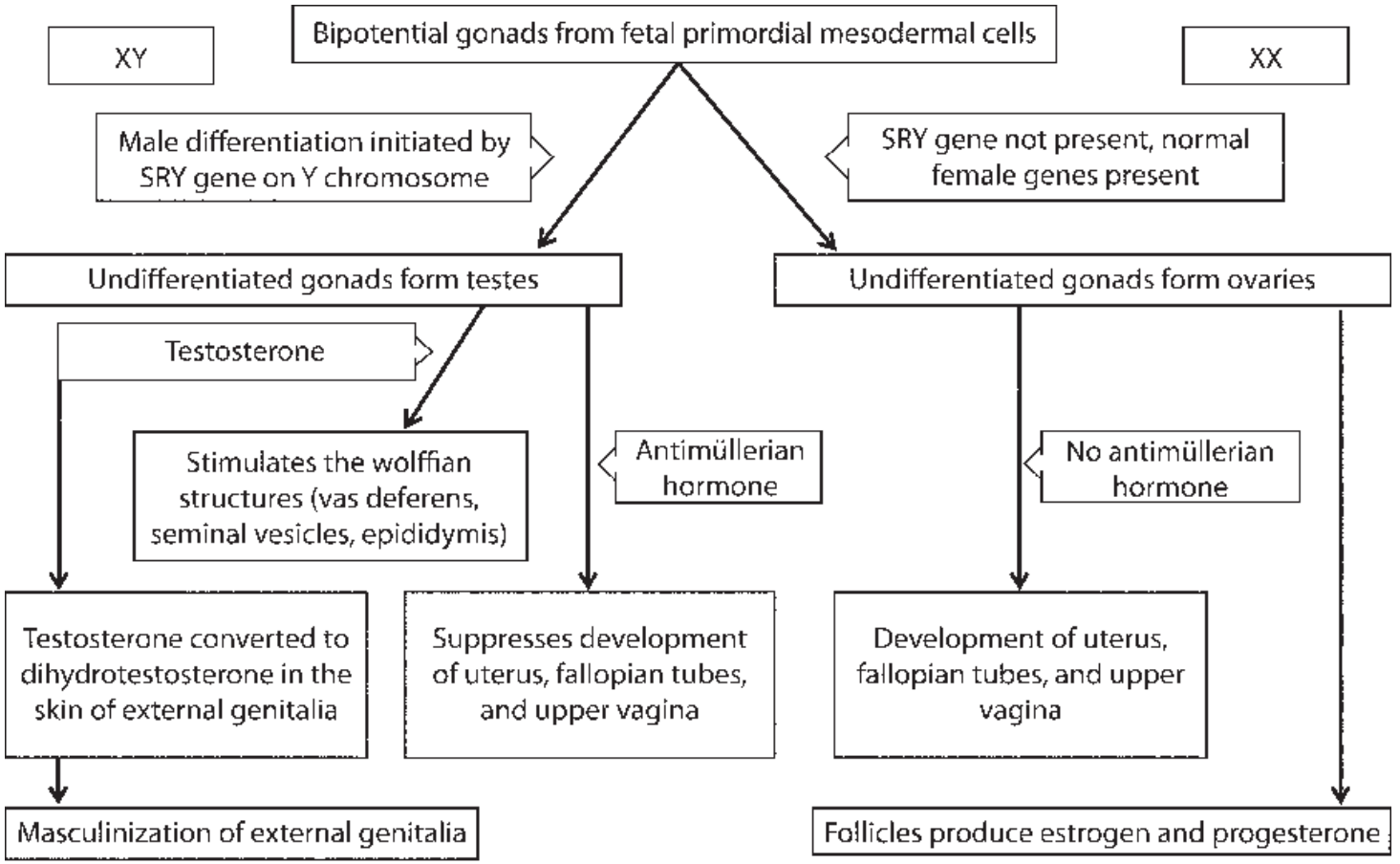
1 – **Chromosomal sex** (presence/absence of a Y chromosome

2 - **Gonadal sex** (primary sex determination): whether the gonads develop as testes or ovaries depends on presence or absence of SRY

3 – **Phenotypic sex** (secondary sex determination) which refers to an individual's sex as determined by their internal and external genitalia, expression of secondary sex characteristics, and behavior.

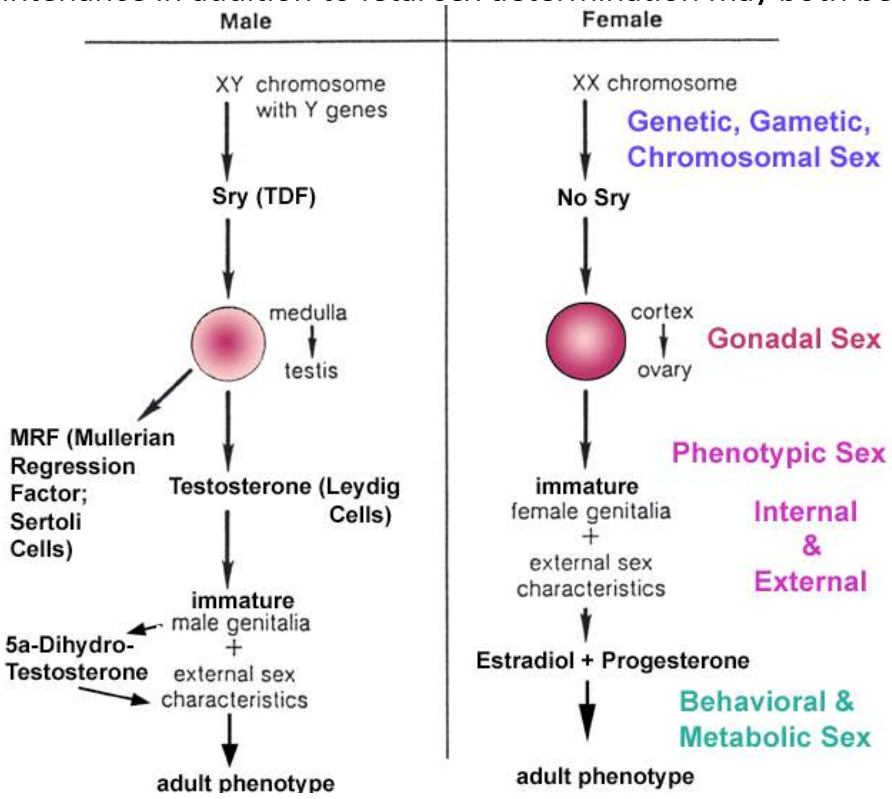


Sex Determination and Sexual Differentiation

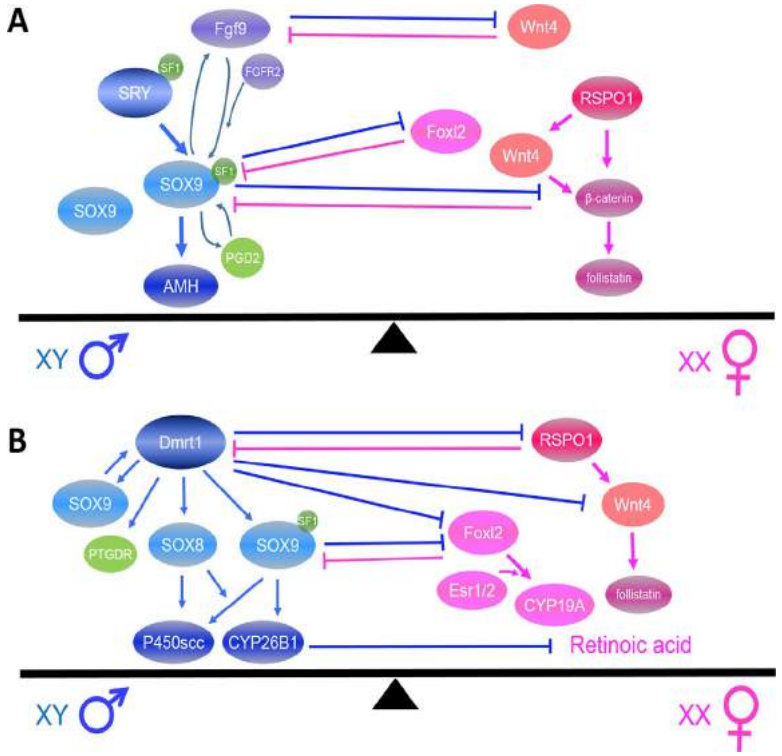


Gonadal sex phenotype can switch even in adulthood

- Recent studies in mice have provided evidence that it is possible for the gonadal sex phenotype to be switched even in adulthood.
- Two key genes, doublesex and mad-3 related transcription factor 1 (Dmrt1) and forkhead box L2 (Foxl2), function in a Yin and Yang relationship to maintain the fates of testes or ovaries in adult mammals
- Mutations in either gene have a dramatic effect on gonadal phenotype (female to male sex reversal in adult Dmrt1 Tg mouse; in humans, deletion of Ch9p with Dmrt1->XY male-to-female sex reversal.
- Thus, adult gonad maintenance in addition to fetal sex determination may both be important for fertility.



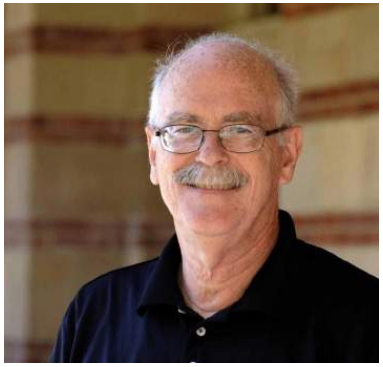
Gonadal sex phenotype can switch even in adulthood



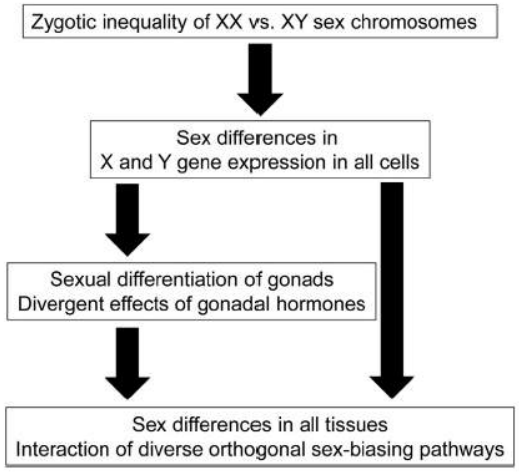
Delicate balance between male and female signaling pathways during sex development both in embryogenesis and adult

Lifelong antagonistic signaling pathways occurring throughout the adult life of both sexes have not yet been fully characterized

Non-gonadal tissue sex phenotypes



Arthur P. Arnold (UCLA)



Rethinking sex determination of non-gonadal tissues

Arthur P. Arnold*
Department of Integrative Biology & Physiology, Laboratory of Neuroendocrinology of the Brain Research Institute, University of California, Los Angeles, CA, United States
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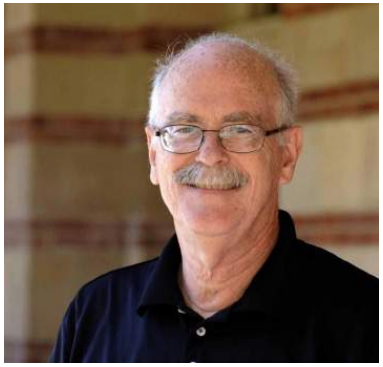
"From the moment of our conception, each of us has a sex. Sex has a major role in determining the physical attributes of our bodies, the structure of our brains, our behavioral tendencies, our susceptibility and reaction to diseases, the environment in which we grow up, our place in society, the attitudes of others towards us, and our conception of self. Although sex may be considered to be determined primarily biologically, our gender (i.e. the social perception and implications of our sex) is arguably equally or more important for our lives. Sex and gender differences are created by an intricate reciprocal interaction of numerous biological and environmental forces."
AP Arnold 2010

For the last 50 years, students have been taught that outside the gonads — where sperm and eggs are produced — cells with XX and XY pairs are functionally equivalent because there is nothing on the X or Y chromosome that acts outside the testes. They've been taught that hormones secreted by the testes and the ovaries, where eggs are produced, are entirely responsible for making the body more masculine or feminine.
However we now know that there are intrinsic biochemical differences between XX and XY cells that affect tissues and organs across the entire body and have a significant impact independent of sex hormones. And medical practitioners must understand these differences to properly treat their patients.
D Page 2016

Non-gonadal tissue sex phenotypes



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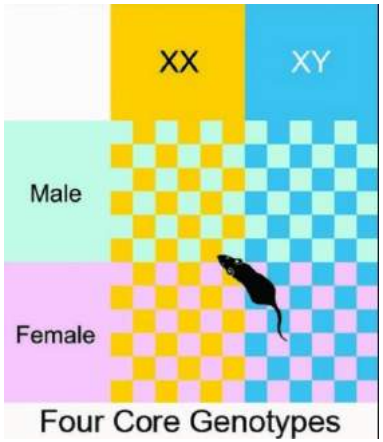

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In species with heteromorphic sex chromosomes, the sex of the individual is established at the time of formation of the zygote, leading to inherent sex differences in expression of sex chromosome genes beginning as soon as the embryonic transcriptome is activated.

The inequality of sex chromosome gene expression causes sexual differentiation of the gonads and of non-gonadal tissues.

The difference in gonad type in turn causes lifelong differences in gonadal hormones, which interact with unequal effects of X and Y genes acting within cells.

Separating the effects of gonadal hormones and sex chromosomes is possible using animal models in which gonadal determination is separated from the sex chromosomes, allowing comparison of XX and XY mice with the same type of gonad.

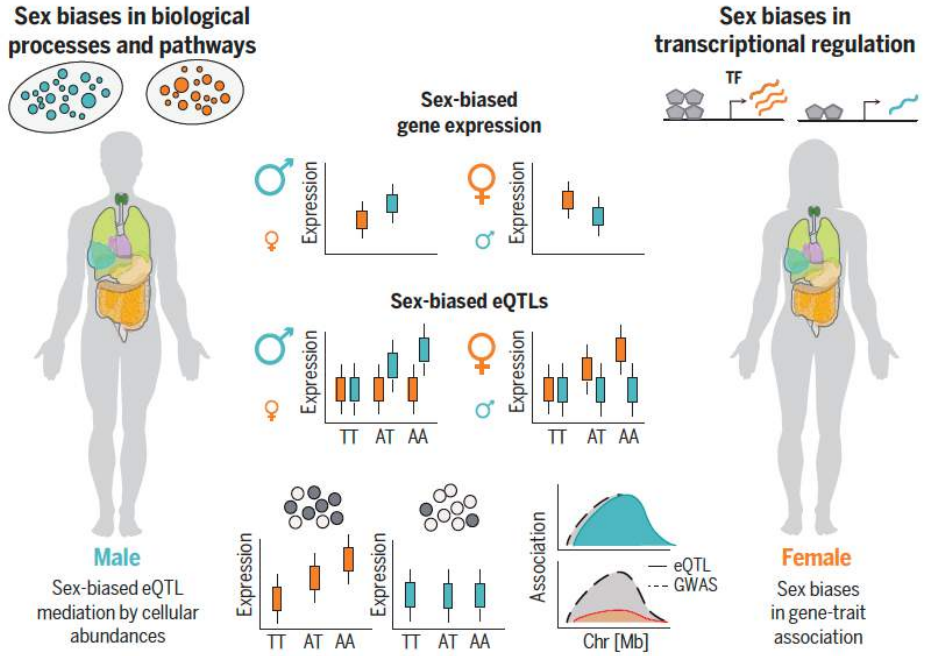
Sex differences caused by gonadal hormones and sex chromosomes affect basic physiology and disease mechanisms in most or all tissues.

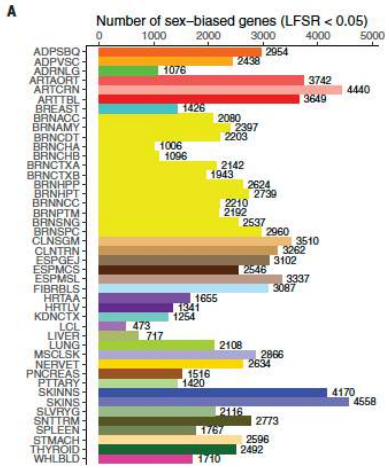
COURS II March 13th

COLLÈGE DE FRANCE 1530

The impact of sex on gene expression across tissues

- Many complex human phenotypes exhibit sex differentiated characteristics.
- The molecular mechanisms underlying these differences remain largely unknown.
- A catalog of sex differences in gene expression and in the genetic regulation of gene expression across 44 human tissue sources surveyed by the Genotype-Tissue Expression project (GTEx, v8 release).
- Sex influences gene expression levels and cellular composition of tissue samples across the human body.
- A total of 37% of all genes exhibit sex-biased expression in at least one tissue.
- Identifed cis expression quantitative trait loci (eQTLs) with sex-differentiated effects and characterized their cellular origin.
- Iintegrating sex-biased eQTLs with genome-wide association study data, we identify 58 gene-trait associations that are driven by genetic regulation of gene expression in a single sex.
- These findings provide an extensive characterization of sex differences in the human transcriptome and its genetic regulation.



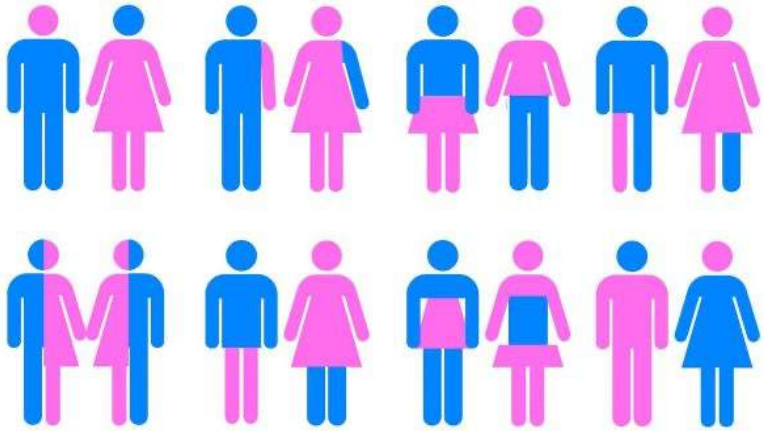


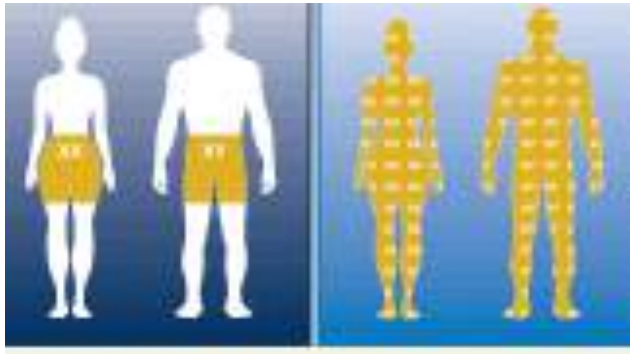
- Sex affects gene expression and its genetic regulation across tissues.
- Sex effects on gene expression were measured in 44 GTEx human tissue sources and integrated with genotypes of 838 subjects.
- Sex-biased expression is present in numerous biological pathways and is associated to sex-differentiated transcriptional regulation.
- Sex-biased expression quantitative trait loci in cis (sex-biased eQTLs) are partially mediated by cellular abundances and reveal gene trait associations.

Oliva et al., Science 369, 1331 (2020)

Biological Sex and Gender Definitions

- The terms “sex” and “gender” are used inconsistently and interchangeably in research on health.
- Sex refers to the biological distinctions between males and females, most often in connection with reproductive functions.
- Gender emphasizes the socially constructed differences between men and women that give rise to masculinity and femininity.
- Intersex traits seem to affect between 1% and 2% of humans at birth.
- Millions of individuals do not conform to the two “sexes” or types that characterize the immense majority of humans, namely the female type (two X chromosomes, ovaries, anatomical features favoring pregnancy and fetal development etc) and the male type (one X and one Y chromosome, a penis and testicles, internal ducts for the transportation of urine and sperm etc.).
- The diversity of forms of sexual development and the atypical types that occur are striking, whether of chromosomal, hormonal or environmental origin (caused by chemical products that disturb the endocrine system or by drugs taken during pregnancy, for instance).





See “How Many Sexes Are There?
P Testard Vaillant (CNRS

Biological Sex and Gender Definitions

The term gender can be applied to individual differences, as well as to cultural, institutional, structural differences.

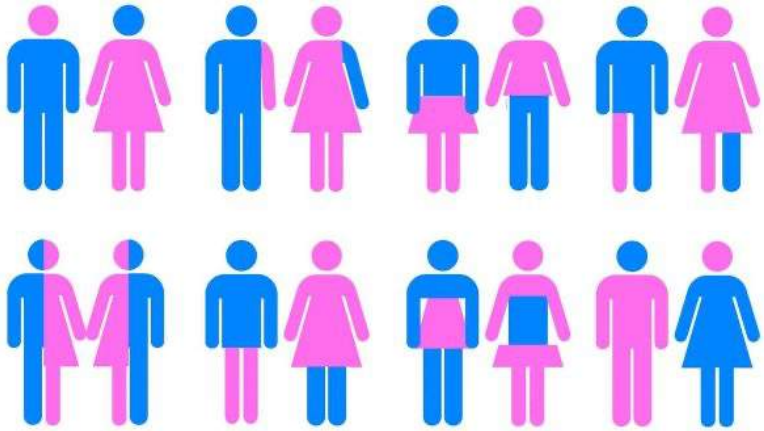
In the 1970s, feminist scholars promoted use of the term gender to draw attention to the reality that not all differences between men and women could be explained by biology.

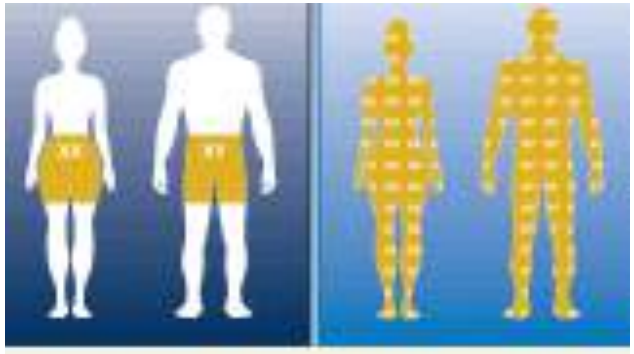
This distinction allowed scholars to counter academic and popular portrayals of the differences between men and women as natural, and by extension, immutable.

Biomedical and social scientists are increasingly calling binary biological sex into question, arguing that sex is a graded spectrum rather than a binary trait. The current uses of the term Biological Sex can thus be confusing!

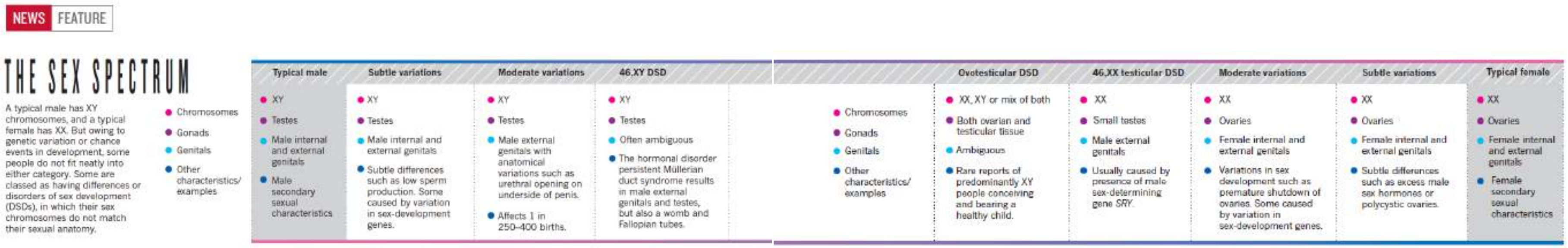
Oxford English Dictionary: sex "tends now to refer to biological differences, while gender often refers to cultural or social ones."

World Health Organization (WHO): "'sex' refers to the biological and physiological characteristics that define men and women" and that "'male' and 'female' are sex categories"





Biological Sex and Gender Definitions



NEWS FEATURE

THE SEX SPECTRUM

A typical male has XY chromosomes, and a typical female has XX. But owing to genetic variation or chance events in development, some people do not fit neatly into either category. Some are classed as having differences or disorders of sex development (DSDs), in which their sex chromosomes do not match their sexual anatomy.

	Typical male	Subtle variations	Moderate variations	46,XY DSD	Ovotesticular DSD	46,XX testicular DSD	Moderate variations	Subtle variations	Typical female
Chromosomes	XY	XY	XY	XY	XX, XY or mix of both	XX	XX	XX	XX
Gonads	Testes	Testes	Testes	Testes	Both ovarian and testicular tissue	Small testes	Ovaries	Ovaries	Ovaries
Genitals	Male internal and external genitals	Male internal and external genitals	Male external genitals with anatomical variations such as urethral opening on underside of penis.	Often ambiguous	Ambiguous	Male external genitals	Female internal and external genitals	Female internal and external genitals	Female internal and external genitals
Other characteristics/ examples	Male secondary sexual characteristics	Subtle differences such as low sperm production. Some caused by variation in sex-development genes.	Affects 1 in 250–400 births.	The hormonal disorder persistent Müllerian duct syndrome results in male external genitals and testes, but also a womb and Fallopian tubes.	Rare reports of predominantly XY people conceiving and bearing a healthy child.	Usually caused by presence of male sex-determining gene *SRY*.	Variations in sex development such as premature shutdown of ovaries. Some caused by variation in sex-development genes.	Subtle differences such as excess male sex hormones or polycystic ovaries.	Female secondary sexual characteristics

NEWS FEATURE

SEX REDEFINED

THE IDEA OF TWO SEXES IS SIMPLISTIC. BIOLOGISTS NOW THINK THERE IS A WIDER SPECTRUM THAN THAT.

E. Heard, March 6th 2023

(*Nature* **518,** 288–291; 2015).

The idea that there are more than two biological sexes is not as recent as you imply

(*Nature* **518,** 288–291; 2015). It emerged in the early 1990s after feminist critics of science joined forces with an intersex activist movement. Their aim was to prevent reinforcement of the artificial two-sex construct by reforming the practice of surgical intervention (see, for example, A. Fausto-Sterling *The Sciences* **33,** 20–24 (1993) and S. J. Kessler *Lessons from the Intersexed* Rutgers Univ. Press, 1998).

These groups pointed out that science is not isolated from society: ideas that stimulate understanding travel into the lab from street activists, literature and varied scholarship, and move back out again. As a result of their efforts, research scientists were pushed into visualizing the previously invisible.

Anne Fausto-Sterling *Brown University, Providence, Rhode Island, USA.*
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Sex is real: Yes, there are just two biological sexes. No, this doesn't mean every living thing is either one or the other

<u>**Paul Griffiths**</u>

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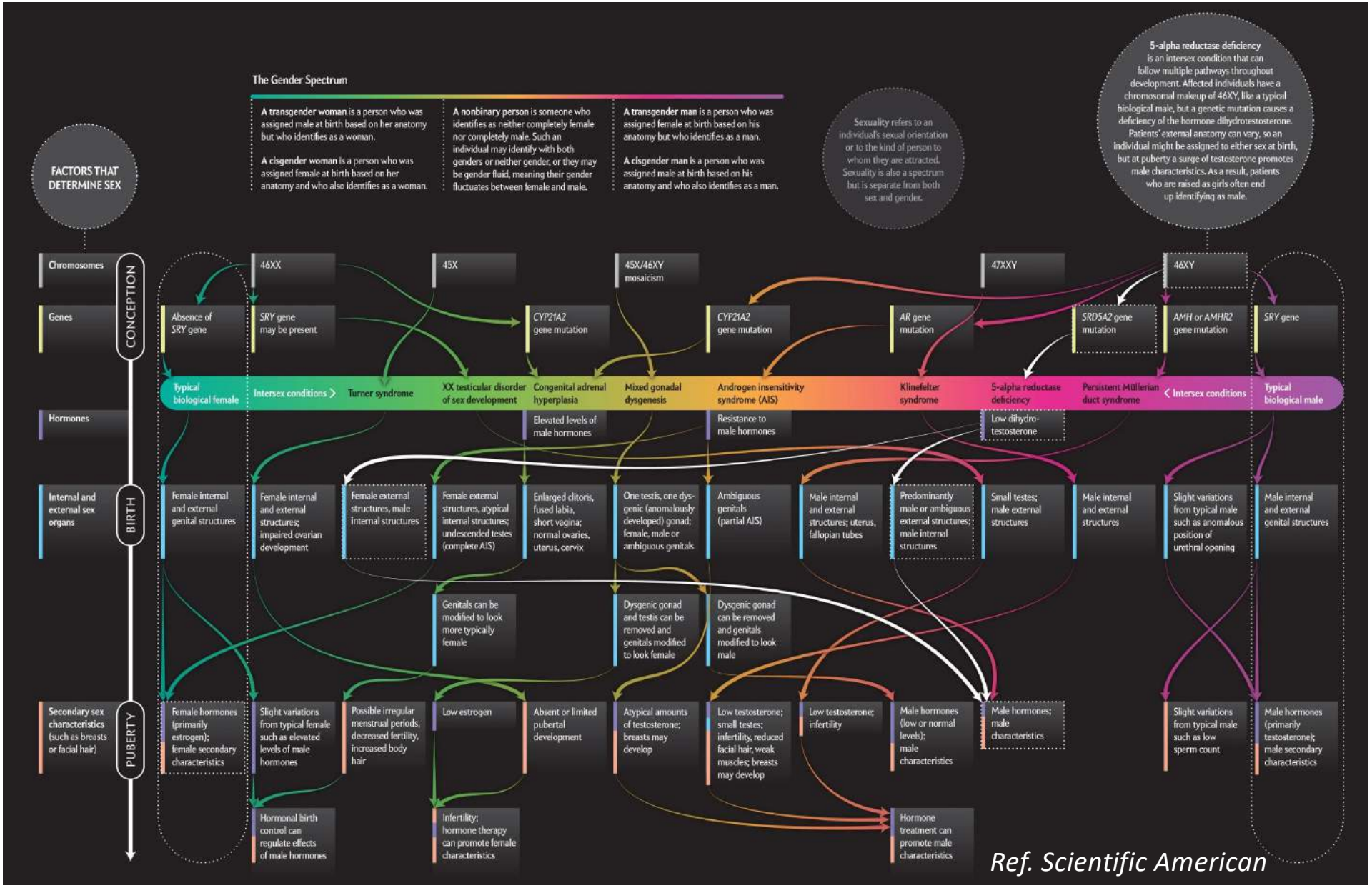

FACTORS THAT DETERMINE SEX
The Gender Spectrum
A transgender woman is a person who was assigned male at birth based on her anatomy but who identifies as a woman.
A cisgender woman is a person who was assigned female at birth based on her anatomy and who also identifies as a woman.
A nonbinary person is someone who identifies as neither completely female nor completely male. Such an individual may identify with both genders or neither gender, or they may be gender fluid, meaning their gender fluctuates between female and male.
A transgender man is a person who was assigned female at birth based on his anatomy but who identifies as a man.
A cisgender man is a person who was assigned male at birth based on his anatomy and who also identifies as a man.
Sexuality refers to an individual's sexual orientation or to the kind of person to whom they are attracted. Sexuality is also a spectrum but is separate from both sex and gender.
5-alpha reductase deficiency is an intersex condition that can follow multiple pathways throughout development. Affected individuals have a chromosomal makeup of 46XY, like a typical biological male, but a genetic mutation causes a deficiency of the hormone dihydrotestosterone. Patients' external anatomy can vary, so an individual might be assigned to either sex at birth, but at puberty a surge of testosterone promotes male characteristics. As a result, patients who are raised as girls often end up identifying as male.
CONCEPTION
BIRTH
PUBERTY
Chromosomes
Genes
Hormones
Internal and external sex organs
Secondary sex characteristics (such as breasts or facial hair)
46XX
45X
45X/46XY mosaicism
47XXY
46XY
Absence of SRY gene
SRY gene may be present
CYP21A2 gene mutation
CYP21A2 gene mutation
AR gene mutation
SRD5A2 gene mutation
AMH or AMHR2 gene mutation
SRY gene
Typical biological female
Intersex conditions
Turner syndrome
XX testicular disorder of sex development
Congenital adrenal hyperplasia
Mixed gonadal dysgenesis
Androgen insensitivity syndrome (AIS)
Klinefelter syndrome
5-alpha reductase deficiency
Persistent Müllerian duct syndrome
Intersex conditions
Typical biological male
Elevated levels of male hormones
Resistance to male hormones
Low dihydro-testosterone
Female internal and external genital structures
Female internal and external structures; impaired ovarian development
Female external structures, male internal structures
Female external structures, atypical internal structures; undescended testes (complete AIS)
Enlarged clitoris, fused labia, short vagina; normal ovaries, uterus, cervix
One testis, one dys-genic (anomalously developed) gonad; female, male or ambiguous genitals
Ambiguous genitals (partial AIS)
Male internal and external structures; uterus, fallopian tubes
Predominantly male or ambiguous external structures; male internal structures
Small testes; male external structures
Male internal and external structures
Slight variations from typical male such as anomalous position of urethral opening
Male internal and external genital structures
Genitals can be modified to look more typically female
Dysgenic gonad and testis can be removed and genitals modified to look female
Dysgenic gonad can be removed and genitals modified to look male
Female hormones (primarily estrogen); female secondary characteristics
Slight variations from typical female such as elevated levels of male hormones
Possible irregular menstrual periods, decreased fertility, increased body hair
Low estrogen
Absent or limited pubertal development
Atypical amounts of testosterone; breasts may develop
Low testosterone; small testes; infertility, reduced facial hair, weak muscles; breasts may develop
Low testosterone; infertility
Male hormones (low or normal levels); male characteristics
Male hormones; male characteristics
Slight variations from typical male such as low sperm count
Male hormones (primarily testosterone); male secondary characteristics
Hormonal birth control can regulate effects of male hormones
Infertility; hormone therapy can promote female characteristics
Hormone treatment can promote male characteristics
Ref. Scientific American

Biological Sex and Gender Definitions

Common terms used in gender medicine

Biological sex. Either of the two main categories (male and female) into which humans and most other species are classified on the basis of their reproductive functions, sex chromosomes, sex hormones, gonads and genitals.

Intersex. Describes individuals born with biological sex characteristics, including chromosome patterns, gonads or genitals, that do not fit typical binary notions of male or female bodies.

Gender. Refers to the socially constructed roles, behaviours, expressions and identities of girls, boys, women, men and gender-diverse people. Gender is neither binary nor fixed. Gender has four dimensions,

- Gender roles: behavioural norms that a society or culture designates as typically masculine or feminine.
- Gender identity: a person's inner sense of self as a woman, man or as a diverse gender.
- Gender relations: refer to how we interact with or are treated by people in the world around us on the basis of our ascribed gender.
- Institutionalized gender: reflects the distribution of power between genders in the political, educational and social institutions in society.

Cisgender. Refers to people whose gender identity corresponds to the sex they were assigned at birth.

Gender dysphoria. The feeling of discomfort or distress occurring when gender identity differs from biological sex.

Transgender. Describes individuals with a gender identity that does not match the sex they were assigned at birth.

Cross-sex hormone therapy or gender-affirming hormone therapy. Hormone therapy involving the administration of sex hormones and other hormonal medications in transgender or gender non-conforming individuals for the purpose of more closely aligning their secondary sexual characteristics with their gender identity.

Biological Sex and Gender Definitions

Received: 1 September 2022 | Revised: 2 December 2022 | Accepted: 2 December 2022
DOI: 10.1002/bies.202200173

BioEssays

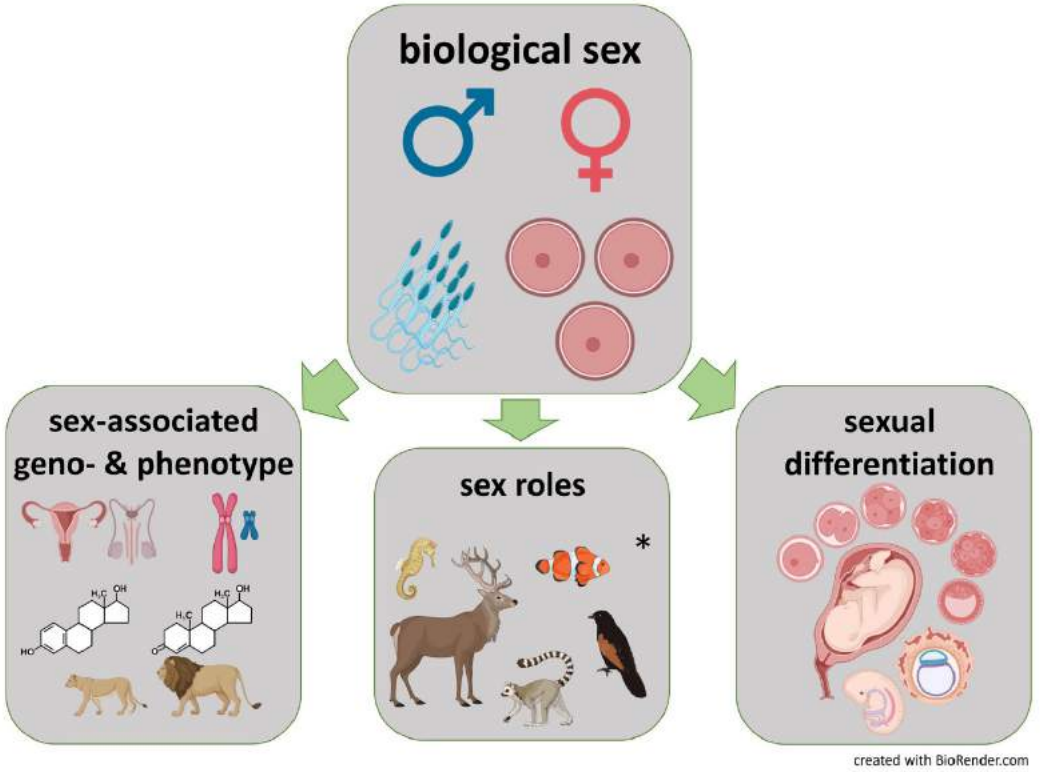
THINK AGAIN
Insights & Perspectives

Biological sex is binary, even though there is a rainbow of sex roles

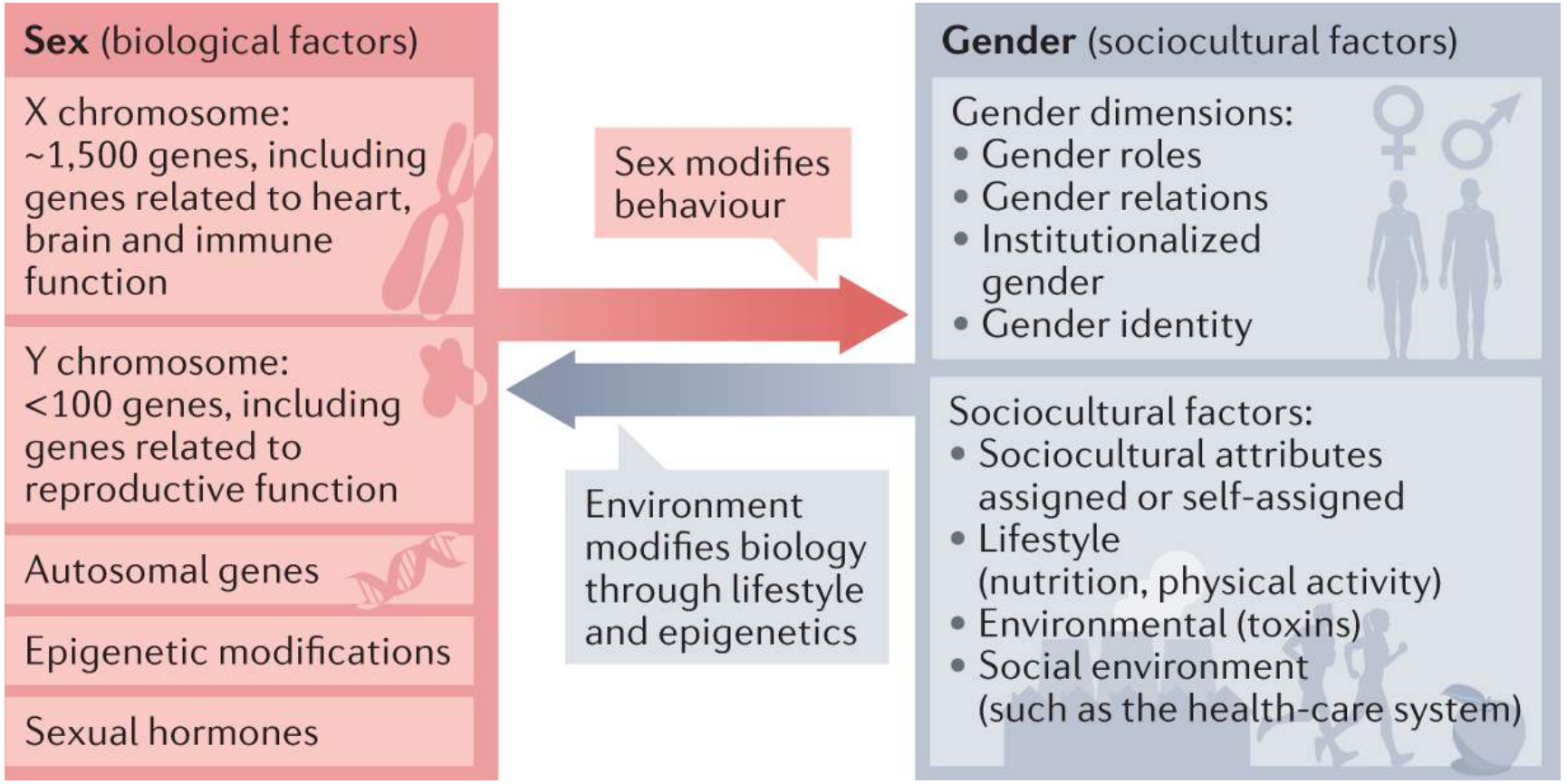
Denying biological sex is anthropocentric and promotes species chauvinism

Wolfgang Goymann[1] | Henrik Brumm[2] | Peter M. Kappeler[3,4]

"While we fully endorse efforts to create a more inclusive environment for gender-diverse people, this does not require denying biological sex. On the contrary, the rejection of biological sex seems to be based on a lack of knowledge about evolution and it champions species chauvinism, inasmuch as it imposes human identity notions on millions of other species. We argue that the biological definition of the sexes remains central to recognising the diversity of life. Humans with their unique combination of biological sex and gender are different from non human animals and plants in this respect. "



Biological Sex and Gender



Sexual Dimorphism and Sexual Selection

See also COURS I, 2018

- In “The Descent of Man, and Selection in Relation to Sex” (1871) Darwin described in detail the mechanism of sexual selection
- He described this form of selection as being based on the advantages some individuals have over others of the same species and sex, exclusively when it came to reproduction.
- He also suggested that it involved two processes: male-male competition and female choice. This theory is used to explain phenomena like sexual dimorphism – when each sex of a species looks distinctly different – and other differences between the sexes like behaviour.
- Darwin attempted to distinguish between the sexes, describing females as being more choosy and passive than males when it comes to mate choice, and that ‘exceptions’ to this were rare.
- These differences in behaviour were believed to explain the development of characteristics that increase the reproductive success of males such as body size, behaviour and ornamentation- to attract females

Sexual Dimorphism and Sexual Selection

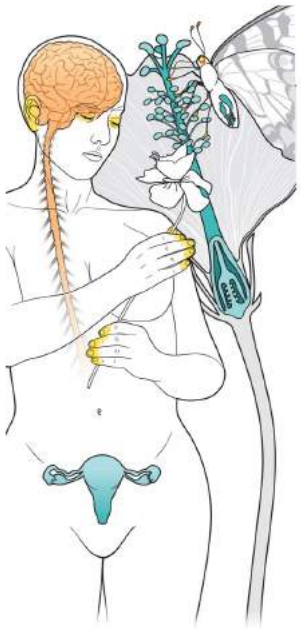
Mate choice, sexual selection, and what Darwin didn't see....

SEXUAL SELECTION

Sexual selection and the ascent of women: Mate choice research since Darwin

Gil G. Rosenthal* and Michael J. Ryan*

Rosenthal *et al.*, *Science* **375**, 281 (2022) 21 January 2022



Mate choice mechanisms across domains of life. Sensory periphery for stimulus detection (yellow), brain for perceptual integration and evaluation (orange), and reproductive structures for postmating choice among pollen or sperm (teal).

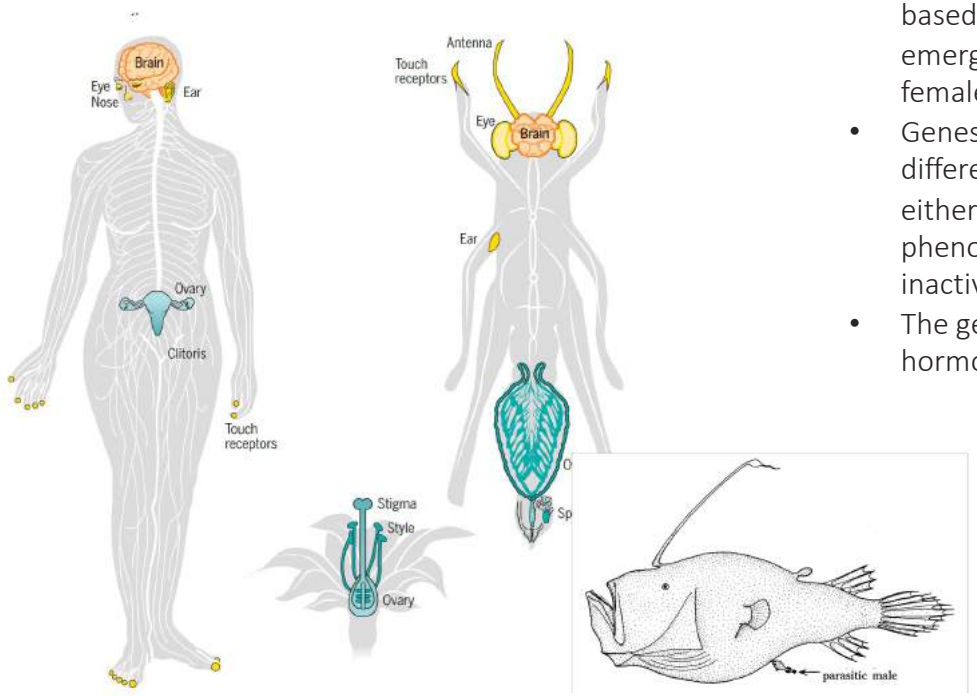


Fig. 1. Analogous mate-choice mechanisms in a flowering plant, an insect, and a mammal. Sensory periphery for stimulus detection (yellow), brain for perceptual integration and evaluation (orange), and reproductive structures for postmating choice among pollen or sperm (teal).

Cells of an Organisms also have a Sex:

- Biological differences between the sexes are also at the biochemical and cellular levels.
- The genetic and molecular bases of a number of sex-based differences in health and human disease, are emerging and some are due to sexual genotype: XX in the female and XY in the male.
- Genes on the sex chromosomes can be expressed differently between males and females due to presence of either single or double copies of genes and other phenomena: different meiotic effects, X-chromosome inactivation, genetic imprinting...
- The genetic identity of a cell of course interacts with the hormonal and external environment too...

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Sexual Dimorphism and Sexual Selection

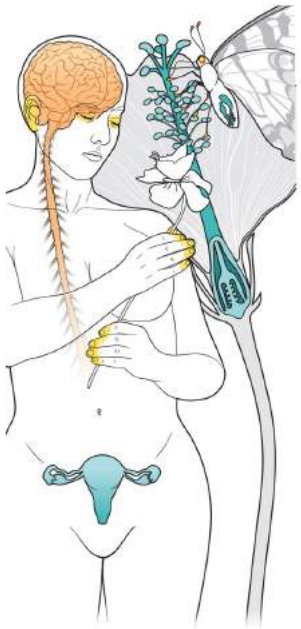
Mate choice, sexual selection, and what Darwin didn't see....

SEXUAL SELECTION

Sexual selection and the ascent of women: Mate choice research since Darwin

Gil G. Rosenthal* and Michael J. Ryan*

Rosenthal *et al.*, *Science* **375**, 281 (2022) 21 January 2022



Mate choice mechanisms across domains of life. Sensory periphery for stimulus detection (yellow), brain for perceptual integration and evaluation (orange), and reproductive structures for postmating choice among pollen or sperm (teal).

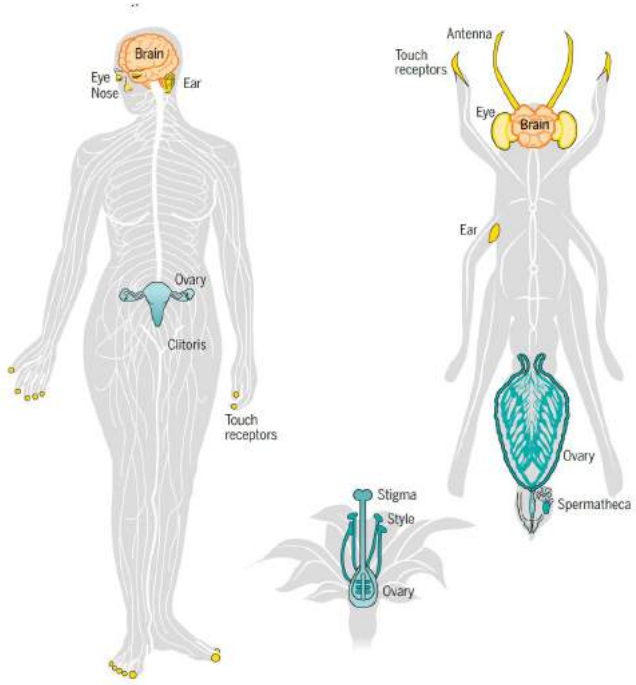
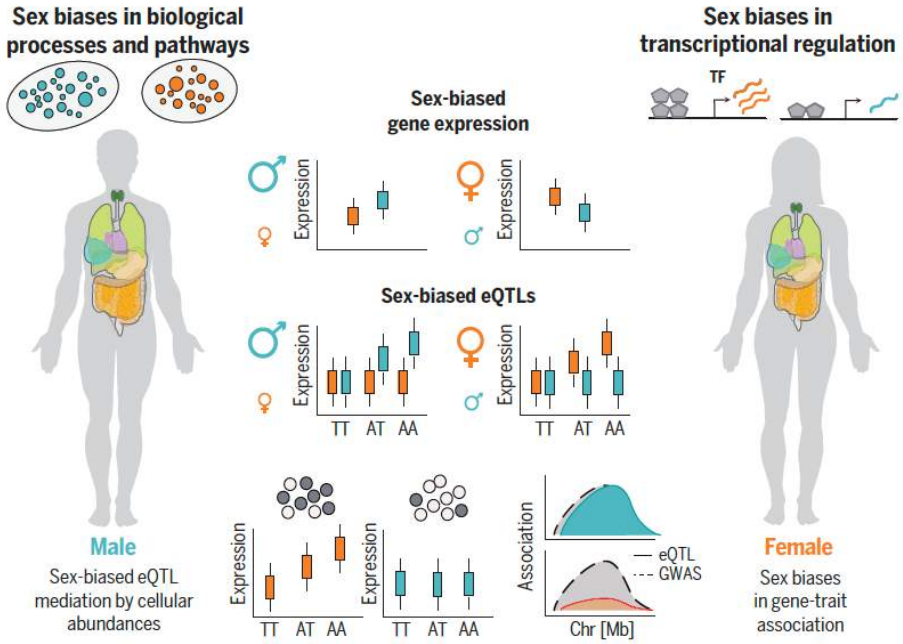


Fig. 1. Analogous mate-choice mechanisms in a flowering plant, an insect, and a mammal. Sensory periphery for stimulus detection (yellow), brain for perceptual integration and evaluation (orange), and reproductive structures for postmating choice among pollen or sperm (teal).

Cells of an Organisms also have a Sex due to sex chromosome and hormonal influences:



COLLÈGE DE FRANCE 1530

Biomedical science has shown a strong sex bias and blindness to sex

"How do we know that research that's primarily done on young, White, healthy males can be extrapolated to women?"

President of the Society for Women's Health Research in Washington, DC, USA, in 2011.

Scientific funding bodies, researchers, and journals have dramatically stepped up their commitments to including sex as a variable in biological research.

Are we sure that sex really is so significant in all aspects of health research?

What evidence do we have that the biological differences between men and women are profound even in the areas in which our anatomies are similar?

THE NEW SCIENCE OF SEX AND GENDER

NOT JUST FOR MEN

Researchers and doctors must dig deeper into gender differences before they can provide women with better treatments

BY MARCIA L. STEFANICK

IN JANUARY 2013 THE U.S. FOOD AND DRUG ADMINISTRATION CUT THE recommended dose of the nation's most popular sleep drug, Ambien, in half for women but not for men. The FDA had determined that 15 percent of the 5.7 million American women using zolpidem products (the active ingredient in Ambien) were experiencing driving impairment eight hours after taking the drug, compared with 3 percent of the 3.5 million male zolpidem users.

Researchers had known for a long time that women, on average, clear zolpidem from their body much more slowly than men do. Indeed, drug metabolism, tolerance, side effects and benefits differ significantly between the average man and woman for many widely prescribed medications, with women having a 50 to 70 percent higher chance of an adverse reaction. Body size, proportion of fat to muscle and a host of other factors, including hormonal influences, account for these differences. But physicians rarely consider these dynamics when writing prescriptions. Ambien, which now comes in bottles with pink (low dose) and blue (original dose) labels, is a rare example of a "sex-specific" medical recommendation.

Drug-dosing problems are just one example of how the health care system is blind to biological sex differences. As a result, women are too often treated like men. Moreover, the system can be blind to gender bias; some disorders are considered "a man's" or "a woman's," even when both sexes suffer from them. Doctors often fail to diagnose stereotypical "male" conditions in women, and vice versa, until the condition has become dangerous.

These problems arise from a serious gap in our understanding of sex differences. The vast majority of animal research has been conducted only on males, mostly on rodents. And women have been grossly underrepresented in human clinical trials. Even when both sexes are included, sex-specific analyses are generally not reported—and because most subjects are men, the findings may not pertain to women. A 2003 review of 258

52 Scientific American, September 2017

Why the preoccupation with Sex? Angela Saini. Perspectives|The art of medicine Volume 400; 10364, 1674-1675, 2022

E. Heard, March 6th 2023

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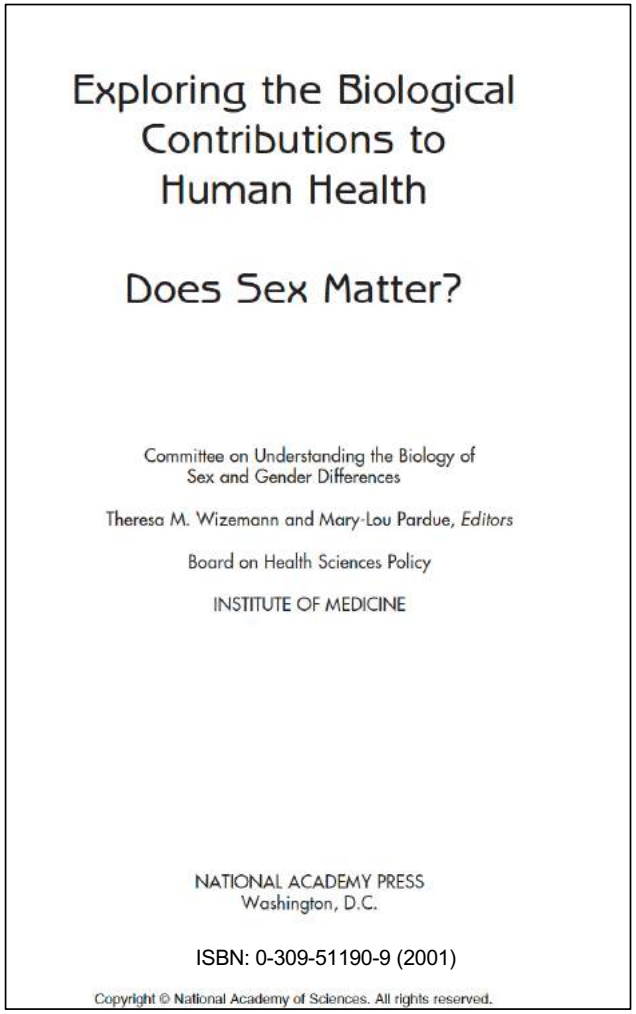
Human Health and Sex Bias in Disease



Exploring the Biological Contributions to Human Health

Does Sex Matter?

Committee on Understanding the Biology of Sex and Gender Differences

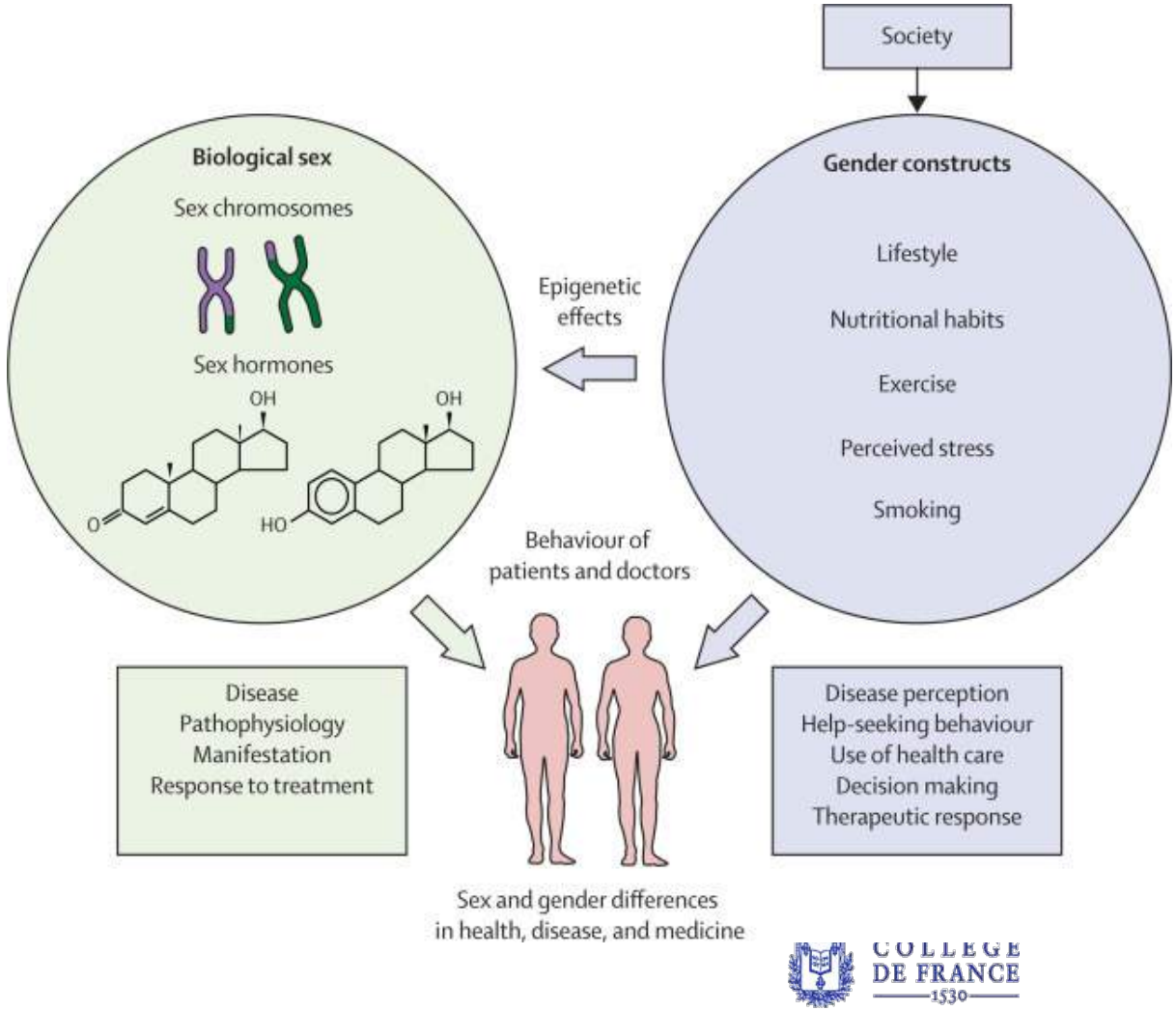
Theresa M. Wizemann and Mary-Lou Pardue, *Editors*

Board on Health Sciences Policy

INSTITUTE OF MEDICINE

NATIONAL ACADEMY PRESS
Washington, D.C.

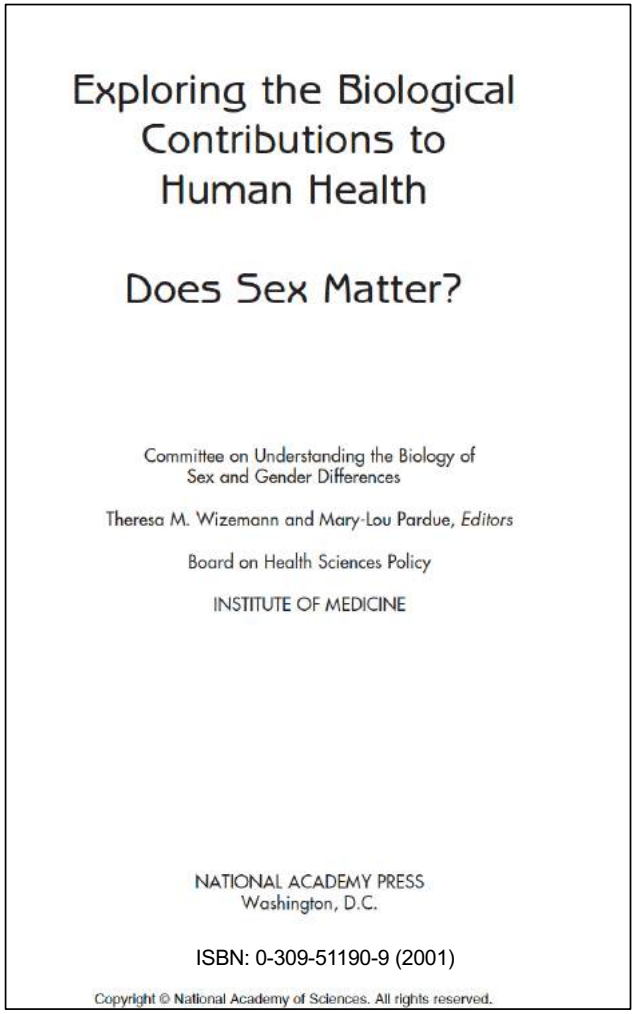
ISBN: 0-309-51190-9 (2001)



E. Heard, March 6th 2023

COLLEGE DE FRANCE 1530

Human Health and Sex Bias in Disease



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Summary of Recommendations

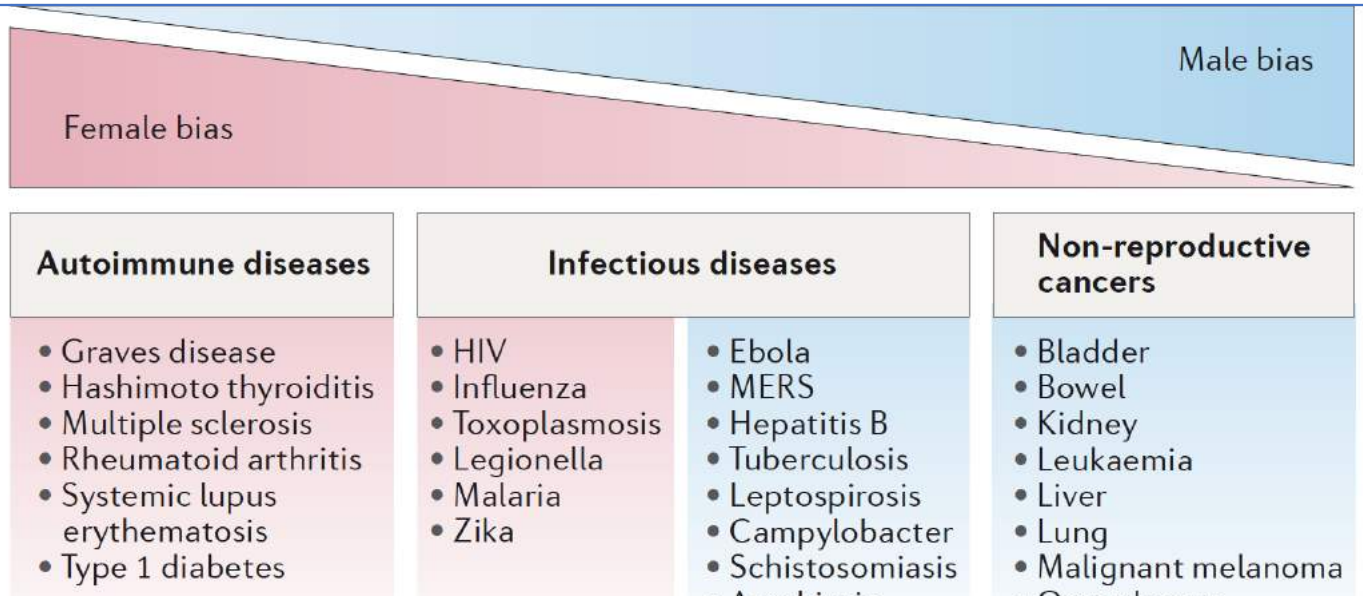
Recommendations for Research

- Promote research on sex at the cellular level.
- Study sex differences from womb to tomb.
- Mine cross-species information.
- Investigate natural variations.
- Expand research on sex differences in brain organization and function.
- Monitor sex differences and similarities for all human diseases that affect both sexes.

Recommendations for Addressing Barriers to Progress

- Clarify use of the terms *sex* and *gender*.
- Support and conduct additional research on sex differences.
- Make sex-specific data more readily available.
- Determine and disclose the sex of origin of biological research materials.
- Conduct and construct longitudinal studies so that the results can be analyzed by sex.
- Identify the endocrine status of research subjects.
- Encourage and support interdisciplinary research on sex differences.
- Reduce the potential for discrimination based on identified sex differences.

Sex Bias in Disease



To achieve effective treatment for all individuals in the era of precision medicine:
Men and women will have to be <u>treated differently,</u>
in order to be protected <u>equally</u>.

guidelines ad drug trials

- Most clinical were typically adjusted for
- Personalized treatment of disease: sex immune responses, infectious an


In utero


Childhood/ pre-puberty


Post-puberty/ adulthood


Old age

Sexual Dimorphism and Human Health

Cancer

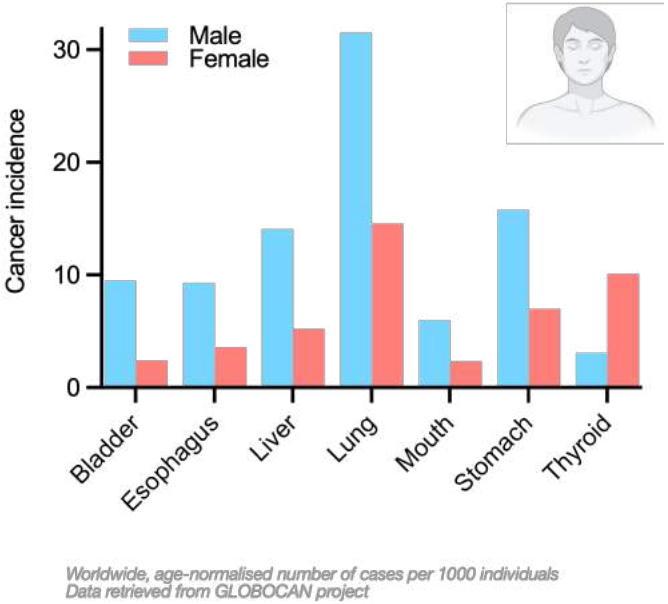
Overall, cancer kills more men than women, but averages mask important sex differences in specific types of cancer. Recognizing disparities could prevent doctors from overlooking or misdiagnosing symptoms.

Women have a higher risk than men of developing right-sided colon cancer, a more aggressive killer than left-sided colon cancer. Diagnosis in women also tends to be more delayed.

More men than women die from lung, colon, kidney and liver cancer. But overall cancer risk is higher for women under age 50.

Being taller is a risk factor for many cancers in both men and women and may account for one third of the greater total cancer risk in men.

Side effects from fluorouracil, a common chemotherapy drug, are significantly worse in women; so are effects from many other cancer drugs.



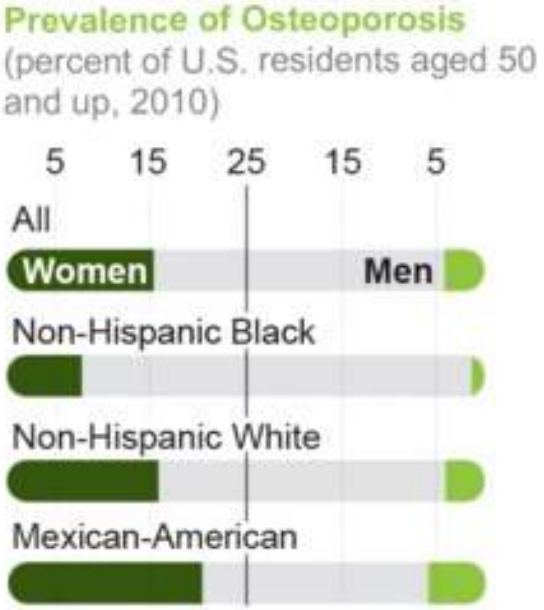
Worldwide, age-normalised number of cases per 1000 individuals
Data retrieved from GLOBOCAN project

Sexual Dimorphism and Human Health

Osteoporosis

Sex and gender differences work both ways. White women are twice as likely as white men to have osteoporosis—fragile-bone—but the risk of death from fractures is 50 percent greater for men.

Women undergo about two thirds of all knee replacements, but there is no evidence that "gender specific" knees, marketed by manufacturers, improve outcomes. Overemphasizing gender differences can be a problem.



Sexual Dimorphism and Human Health

Autoimmune Disease

Certain thyroid autoimmune illnesses such as Hashimoto's disease and Graves' disease are 7 to 10 times higher in women; so is lupus.

Rheumatoid arthritis, multiple sclerosis and scleroderma are at least 2 to 3 times higher in women.

More women than men are infected by herpes simplex virus 2.

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Sexual Dimorphism and Human Health

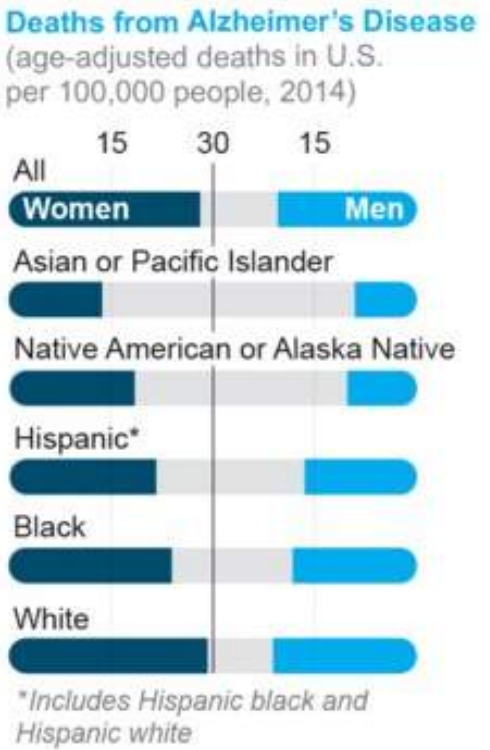
The Brain

Twice as many women as men are diagnosed with anxiety or depression.

Almost two thirds of Americans with Alzheimer's Disease are women.

The *APOE4* gene is more strongly linked to the disease in women. X and Y chromosomes may also play a role.

The number of older U.S. women dying of Alzheimer's is now greater than all U.S. women who die of breast cancer.



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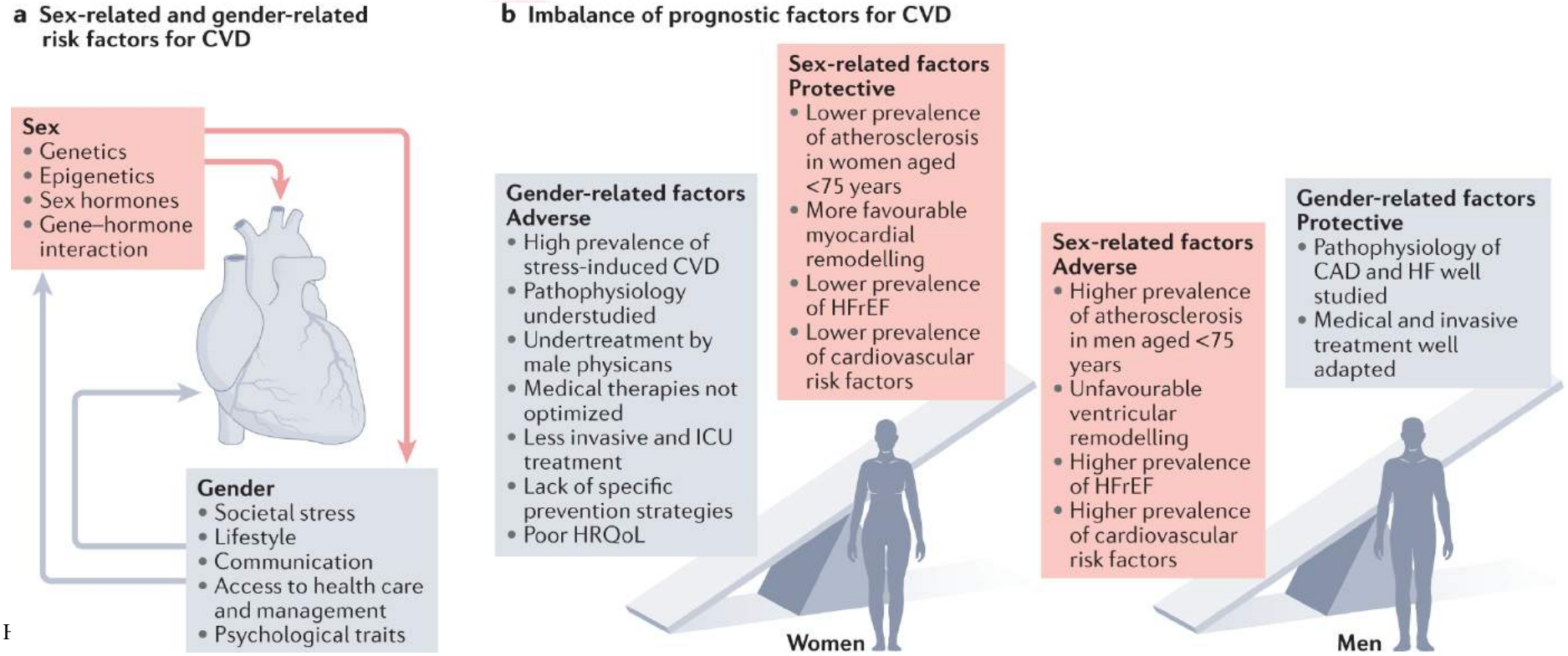
Sexual Dimorphism and Human Health

The Heart

Heart complications often take different forms in women and men. Heart failure in women is more likely to result from left ventricle walls that stiffen and thicken (*illustration*). Among electrical problems, an irregular heartbeat is more common in men, while rapid heartbeat is more common in women—and certain drugs can make the condition life-threatening. Heart valve diseases vary, too. Blood clotting is greater in women, which can affect treatments; that trait may have evolved to prevent excess blood loss during childbirth.

The genetic and hormonal differences between females and males allow for the female cardiovascular system to adapt to changes necessary to sustain a viable foetus, including increases in blood volume, autonomic regulation of blood pressure, and cardiac dynamics, i.e. general cardiovascular function.



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Sexual Dimorphism and Human Health

The Heart

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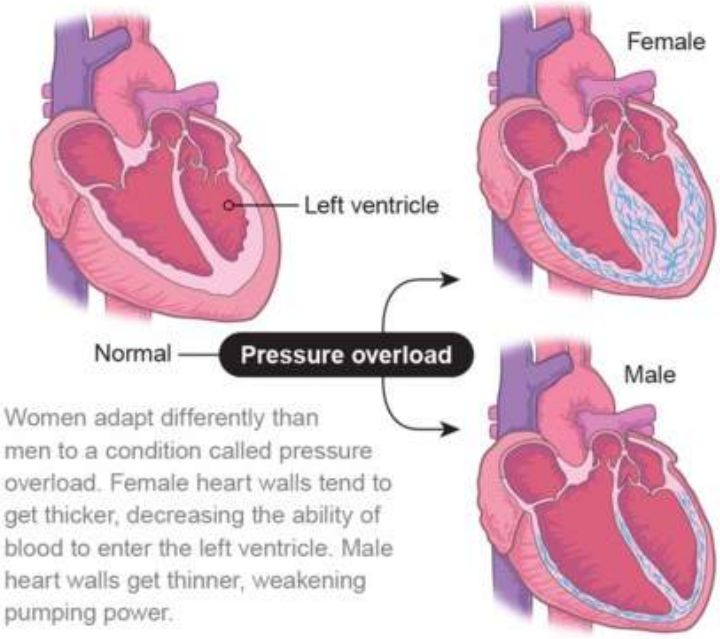
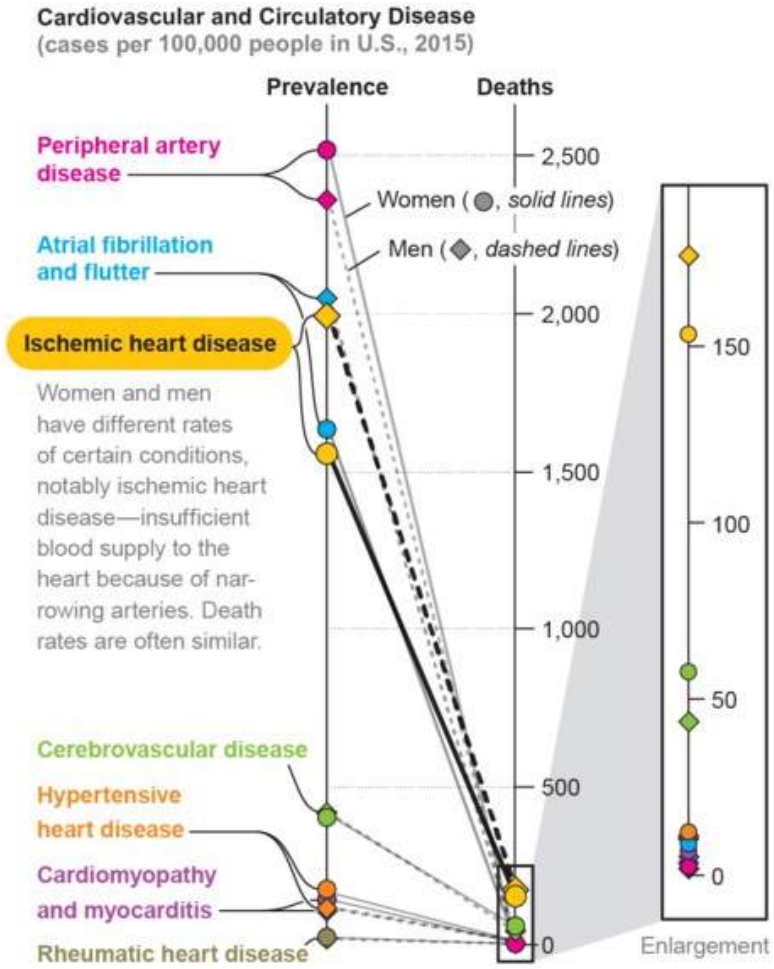


Women adapt differently than men to a condition called pressure overload. Female heart walls tend to get thicker, decreasing the ability of blood to enter the left ventricle. Male heart walls get thinner, weakening pumping power.

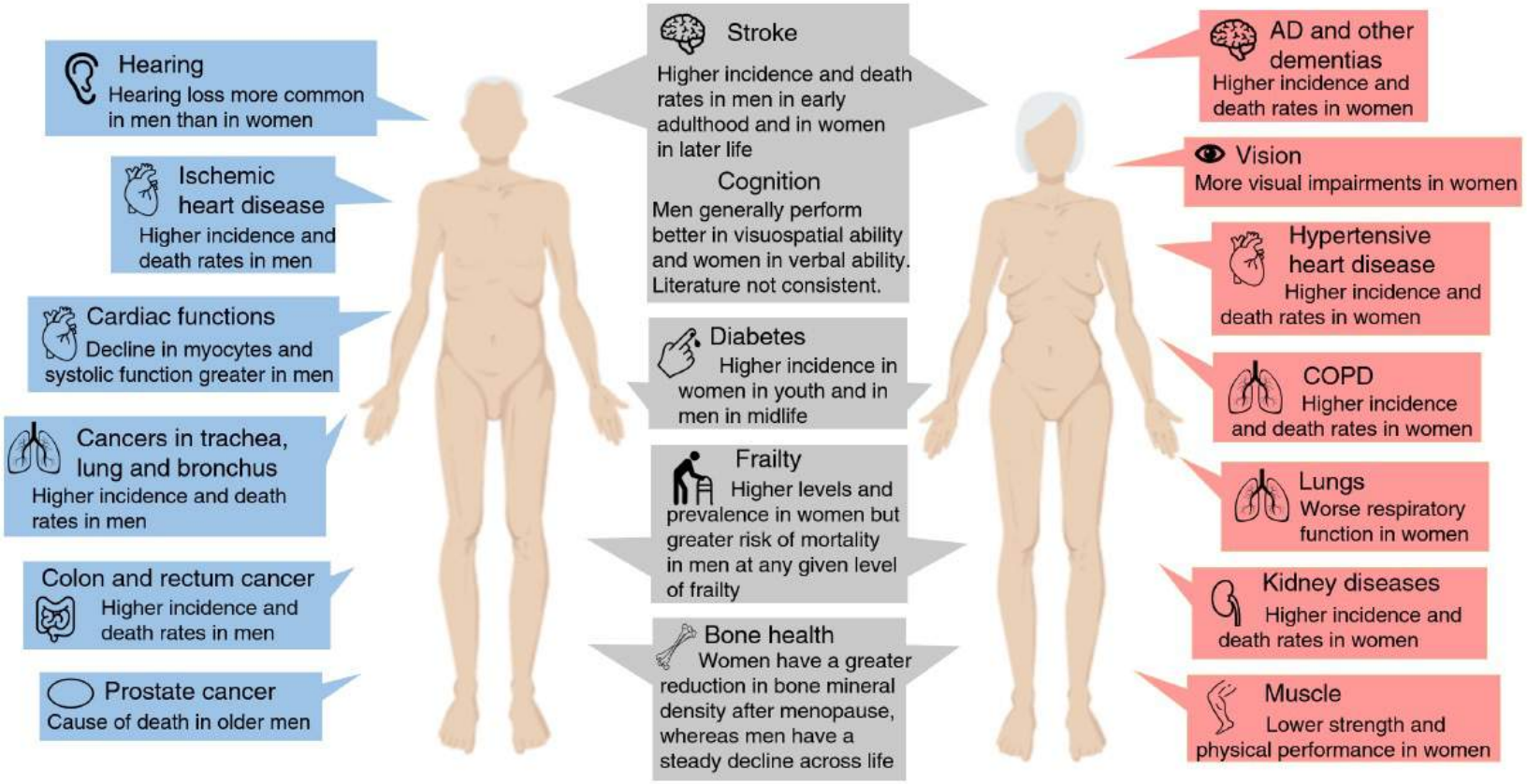


E. Heard, March 6th 2023

Sexual Dimorphism and Human Health

Ageing

Overview of the most significant sex differences in age-related diseases, functioning and frailty.



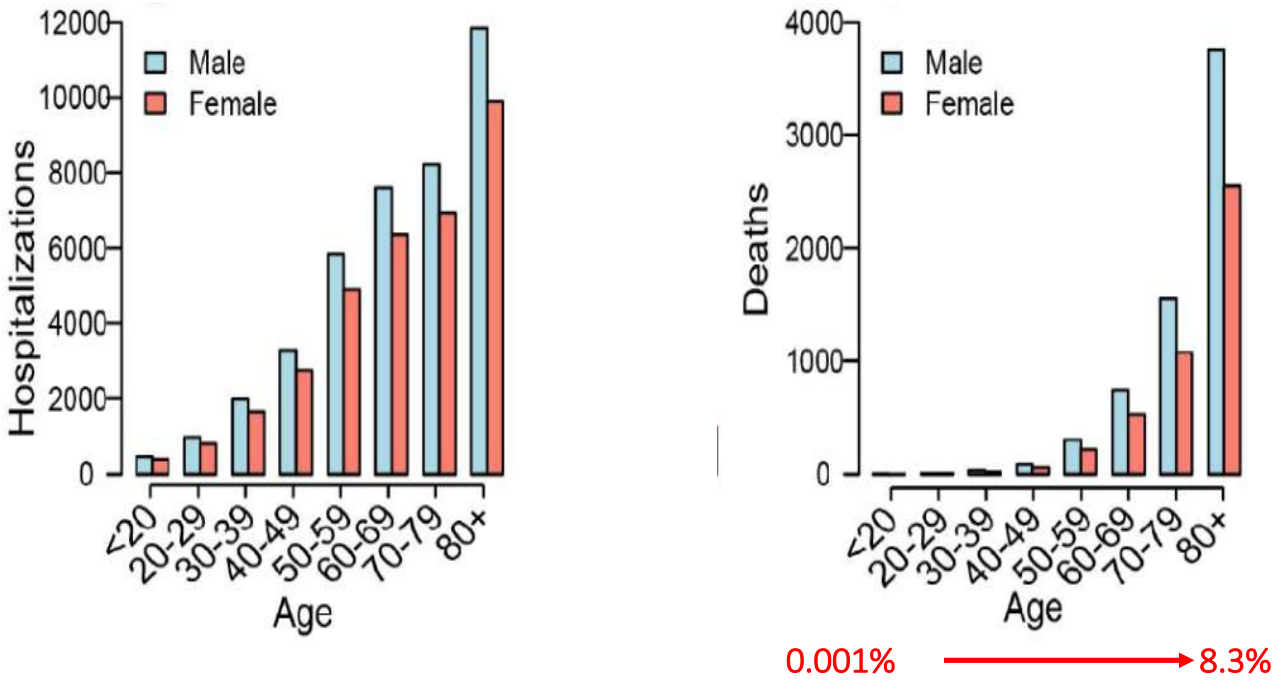
Abbreviations: AD, Alzheimer's disease; COPD, chronic obstructive pulmonary disease.

Hagg and Jylhava. eLife 2021;10:e63425. DOI: https://doi.org/10.7554/eLife.63425

Sexual Dimorphism and Human Health

Infectious Disease

COVID-19 French data / Données françaises



Courtesy of Alain Fischer

H. Salje et al, Science 2020

Sexual Dimorphism and Human Health

Infectious Disease

Considering how biological sex impacts immune responses and COVID-19 outcomes

Eileen P. Scully, Jenna Haverfield, Rebecca L. Ursin, Cara Tannenbaum and Sabra L. Klein

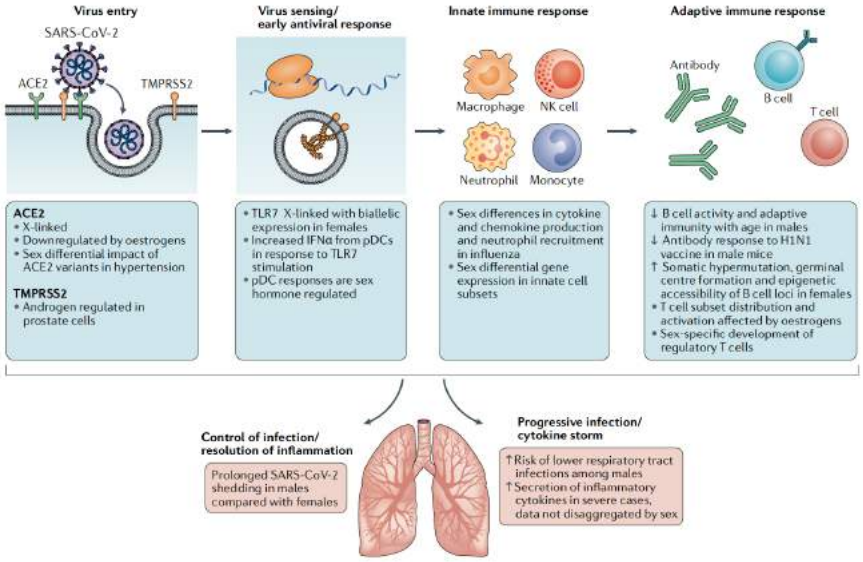


Fig. 2 | **Known sex differences that may impact immune responses to SARS-CoV-2 and COVID-19 progression.** An illustrative summary of the sequence of events in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the associated immune responses. Broadly speaking (from left to right), there are the initial steps of virus entry, innate recognition of the virus with activation of antiviral programmes, the recruitment of innate immune cells and induction of an adaptive immune response. These major steps culminate either in successful control of infection and pathogen elimination or in a pathological inflammatory state. Sex differences that may be operative at multiple points along these pathways are indicated in the blue boxes. ACE2, angiotensin-converting enzyme 2; H1N1, H1N1 influenza virus; IFNα, interferon-α; NK, natural killer; pDC, plasmacytoid dendritic cell; TLR7, Toll-like receptor 7; TMPRSS2, transmembrane protease serine 2.

COVID-19 outcomes

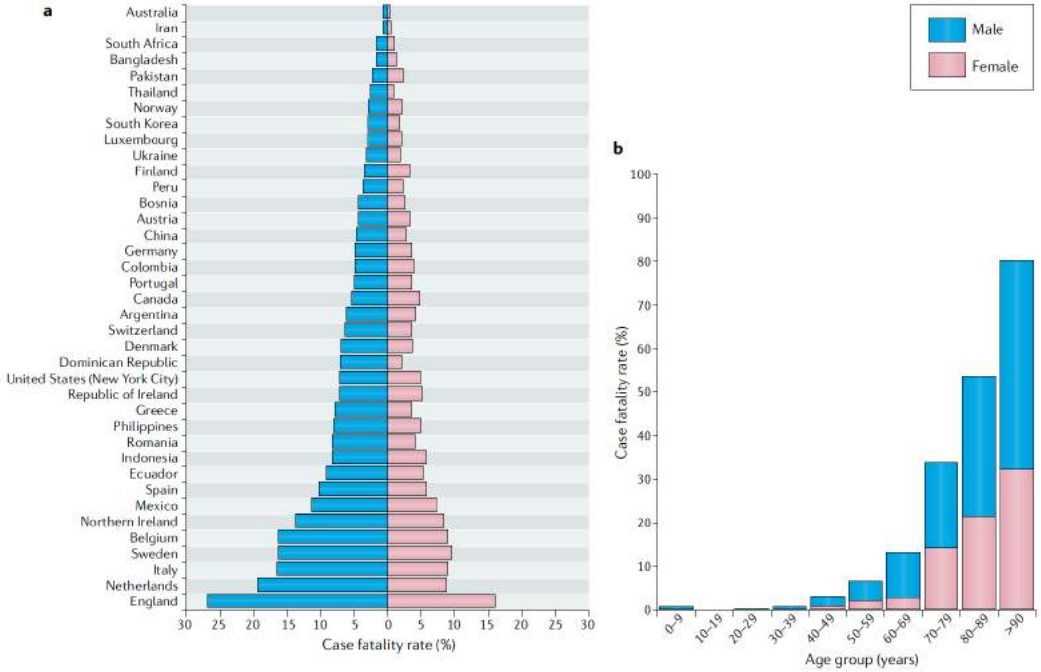


Fig. 1 | **Comparative analyses of COVID-19 case fatality rates by country, sex and age. a** | COVID-19 case fatality rates (CFRs) for males and females across 38 countries or regions reporting sex-disaggregated data on COVID-19 cases and deaths. CFR was calculated as the total number of deaths divided by the total number of cases for each sex multiplied by 100. The male CFR is higher than the female CFR in 37 of the 38 regions, with an average male CFR 1.7 times greater than the average female CFR ($P < 0.0001$, Wilcoxon signed rank test). **b** | Average COVID-19 CFRs for males and females stratified by age. The data represent 12 countries currently reporting sex- and age-disaggregated data on COVID-19 cases and deaths (Australia, Columbia, Denmark, Italy, Mexico, Norway, Pakistan, Philippines, Portugal, Spain, Switzerland and England). The COVID-19 CFR increases for both sexes with advancing age, but males have a significantly higher CFR than females at all ages from 30 years ($P < 0.05$, Wilcoxon signed rank test). The data were obtained from Global Health 50/50 and official government websites of each respective country on 7 May and 8 May 2020. For more information on the data source for a specific country, please contact the corresponding author.

Sexual Dimorphism and Human Health

Lifespan

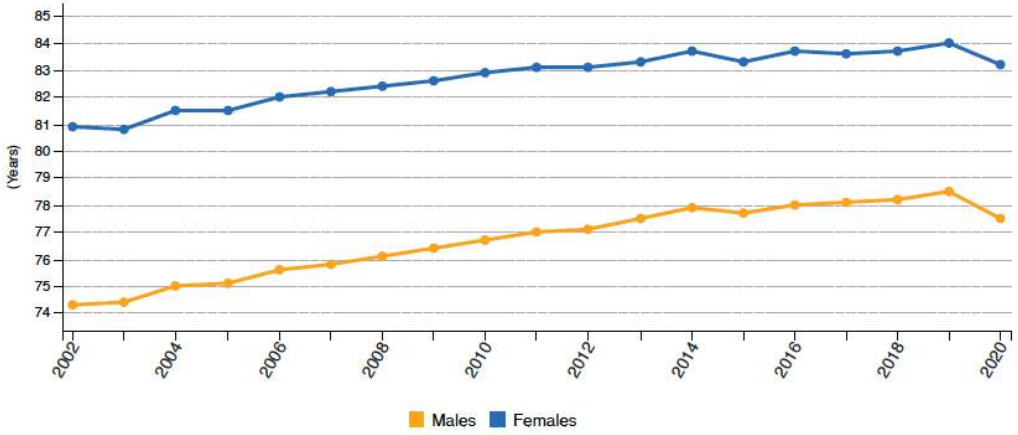
Women live longer than men around the world, regardless of culture or socioeconomic status

Life expectancy higher for women in all EU regions

On the occasion of World Children´s Day on 20th November 2022, Eurostat highlights data on life expectancy at birth which is the average number of years a newborn is expected to live based on current mortality rates across people of all ages.
In 2020, life expectancy of a female newborn in the EU was 83.2 years, 5.7 years higher than for a male newborn (77.5 years).

Data shows that life expectancy is higher for women than for men in every single region of the EU. In 2020, the highest levels of life expectancy at birth for females were in the French island region of Corse (87.0 years). More generally, newborn girls in Spanish, French and Italian regions were expected to live longest.

Life expectancy at birth in the EU, 2002-2020



Note: The y-axis is broken. 2010, 2011, 2012, 2014, 2015, 2017 and 2019: breaks in series. 2018, 2019 and 2020: estimate, provisional.
Source: Eurostat (online data code: demo_mlexpec)

E. Heard, March 6th 2023

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Sexual Dimorphism and Human Health

Lifespan

Women live longer than men around the world, regardless of culture or socioeconomic status

Life expectancy is increasing

Horizontally the chart shows a staggering increase in the proportion of people over 65. From representing only 5 percent of the population in 1950 to 9 percent today, this cohort is expected to reach 23 percent by 2100. Supporting this population shift will require profound changes in policies, institutions, and practice.

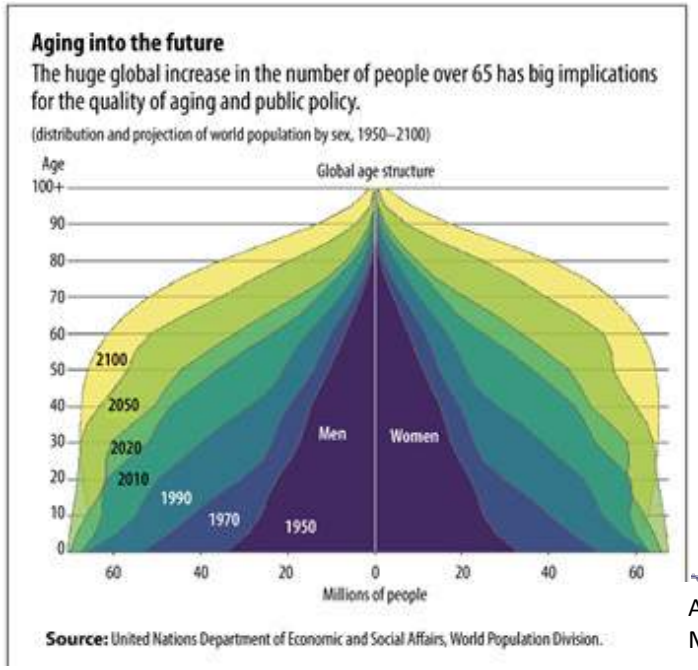
Vertically , however, the chart tells a different story, highlighting not aging, but longevity. From this perspective, children born today have much more time ahead of them than past generations. The likelihood of living into old age has increased, as has the peak of the pyramid, changing what constitutes "old."

Life expectancy at birth by sex for the world, SDG regions, and selected groups of countries, 1990, 2021 and 2050

	Life expectancy at birth (years)								
	1990			*2021*			*2050*		
Region	*Males*	*Females*	*Both sexes*	*Males*	*Females*	*Both sexes*	*Males*	*Females*	*Both sexes*
World	**61.5**	**66.5**	**64.0**	**68.4**	**73.8**	**71.0**	**74.8**	**79.8**	**77.2**
Sub-Saharan Africa	47.3	51.2	49.2	57.8	61.6	59.7	64.3	69.1	66.7
Northern Africa and Western Asia	61.7	67.0	64.3	69.7	74.8	72.1	76.0	80.8	78.3
Central and Southern Asia	58.1	59.9	58.9	65.9	69.6	67.7	74.9	79.4	77.1
Eastern and South-Eastern Asia	65.6	70.7	68.1	73.6	79.6	76.5	79.4	84.1	81.7
Latin America and the Caribbean	64.6	70.9	67.7	68.8	75.8	72.2	78.1	83.1	80.6
Australia/New Zealand	73.7	79.8	76.8	82.7	85.6	84.2	85.4	88.6	87.0
Oceania*	60.3	65.5	62.5	64.6	70.1	67.1	68.4	74.9	71.6
Europe and Northern America	69.7	77.4	73.6	73.9	80.4	77.2	81.6	86.1	83.8
Least developed countries	48.7	51.6	50.1	61.7	66.5	64.1	67.8	73.5	70.6
Landlocked developing Countries	49.0	53.5	51.2	61.0	66.5	63.7	67.4	73.4	70.3
Small island developing States	63.4	67.9	65.6	68.0	73.9	70.8	74.1	80.0	77.0

*excluding Australia and New Zealand

UN World Population Prospects, 2022



Andrew Scott, International Monetary Fund March 2020

Sexual Dimorphism and Human Health

Lifespan

Women live longer than men around the world, regardless of culture or socioeconomic status

Women live longer than men even during severe famines and epidemics

Virginia Zarulli[a,b], Julia A. Barthold Jones[a,b], Anna Oksuzyan[c], Rune Lindahl-Jacobsen[a,b], Kaare Christensen[a,b,d,e], and James W. Vaupel[a,b,f,g,1]

[a]Max Planck Odense Center on the Biodemography of Aging, University of Southern Denmark, DK-5230 Odense, Denmark; [b]Department of Public Health, University of Southern Denmark, DK-5000 Odense, Denmark; [c]Max Planck Research Group Gender Gaps in Health and Survival, Max Planck Institute for Demographic Research, 18057 Rostock, Germany; [d]Department of Clinical Genetics, Odense University Hospital, DK-5000 Odense, Denmark; [e]Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, DK-5000 Odense, Denmark; [f]Max Planck Institute for Demographic Research, 18057 Rostock, Germany; and [g]Duke University Population Research Institute, Duke University, Durham, NC 27708

Contributed by James W. Vaupel, November 22, 2017 (sent for review February 6, 2017; reviewed by Tommy Bengtsson and France Mesle)

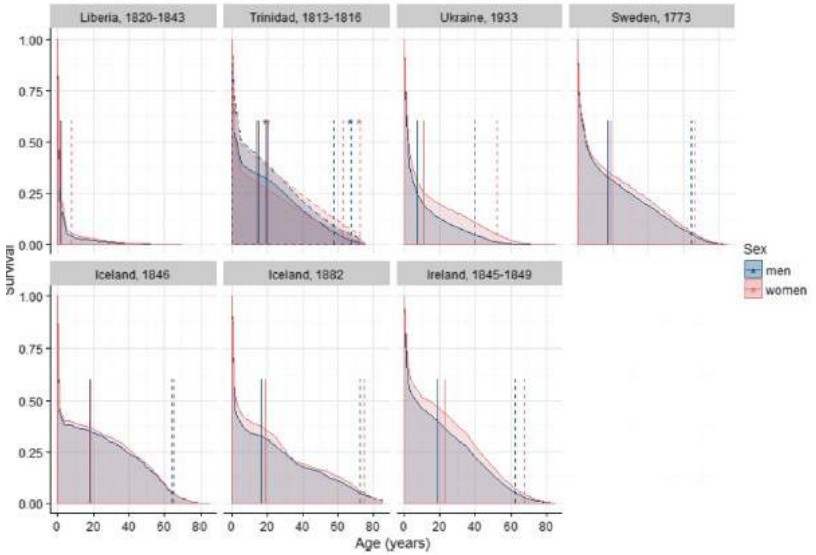


Fig. 1. Survival curves (shaded areas), life expectancies (solid vertical lines), and ages at which only 5% of a synthetic same-sex cohort would still be alive (dashed vertical lines) for seven high-mortality populations. For Trinidad, dashed survival curves and vertical lines with asterisks represent estimated upper bounds. Source: authors' calculations based on published data from ref. 25 for Liberia, from ref. 26 for Trinidad, from ref. 28 for Ukraine, from ref. 31 for Ireland, and from the Human Mortality Database (www.mortality.org) for Sweden and Iceland.

Women live longer than men in nearly all populations today.
Some research focuses on the biological origins of the female advantage; other research stresses the significance of social factors.
We studied male–female survival differences in populations of slaves and populations exposed to severe famines and epidemics.
We find that even when mortality was very high, women lived longer on average than men.
Most of the female advantage was due to differences in mortality among infants: baby girls were able to survive harsh conditions better than baby boys.
These results support the view that the female survival advantage is modulated by a complex interaction of biological environmental and social factors.

COLLÈGE DE FRANCE 1530

Population-wide Analyses of Disease in Men and Women

ARTICLE

https://doi.org/10.1038/s41467-019-08475-9 OPEN

Population-wide analysis of differences in disease progression patterns in men and women

David Westergaard[1], Pope Moseley[1], Freja Karuna Hemmingsen Sørup[1,2], Pierre Baldi[3] & Søren Brunak[1]

Sex-stratified medicine is a fundamentally important, yet understudied, facet of modern medical care. A data-driven model for how to systematically analyze population-wide, longitudinal differences in hospital admissions between men and women is needed. Here, we demonstrate a systematic analysis of all diseases and disease co-occurrences in the complete Danish population using the ICD-10 and Global Burden of Disease terminologies. Incidence rates of single diagnoses are different for men and women in most cases. The age at first diagnosis is typically lower for men, compared to women. Men and women share many disease co-occurrences. However, many sex-associated incongruities not linked directly to anatomical or genomic differences are also found. Analysis of multi-step trajectories uncover differences in longitudinal patterns, for example concerning injuries and substance abuse, cancer, and osteoporosis. The results point towards the need for an increased focus on sex-stratified medicine to elucidate the origins of the socio-economic and ethological differences.

Sex-stratified differences found in this systematic analysis of all diseases and disease co occurrences in the Danish population using the ICD-10 and Global Burden of Disease terminologies

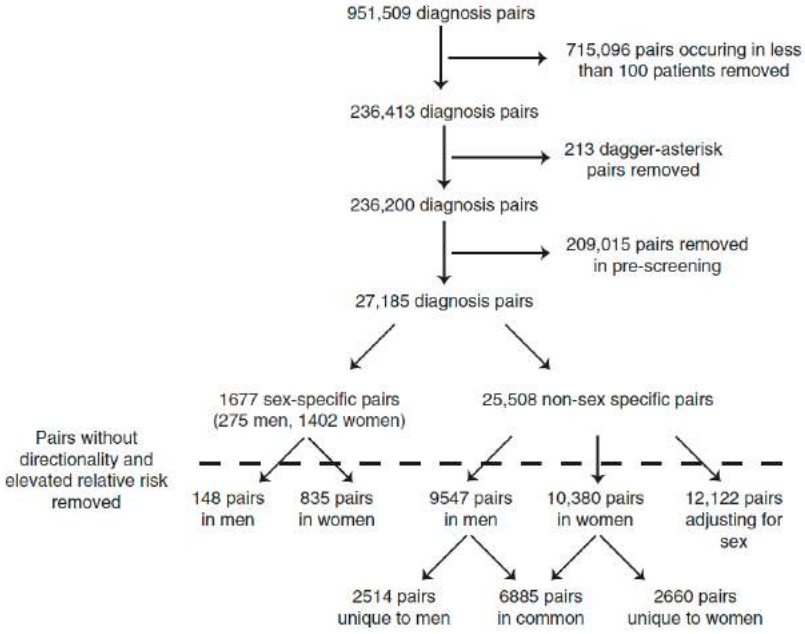


Fig. 2 Diagnosis co-occurrences found in population-wide data from 6,909,676 patients. 951,509 ICD-10 level 3 diagnosis pairs were found to occur in the population; of these, a large number were filtered out due to low frequency ($N < 100$), dagger–asterisk combinations, or due to not passing the crude estimate of the relative risk. The standard method for calculating a confidence interval was applied [illegible] pre-screening Lectich. Post-filtering 27,185 diagnosis pairs remained comprising 1360 unique diagnoses. Of these, 275 pairs involved a male-s[illegible] diagnosis and 1402 a female-specific diagnosis

E. Heard, March 6th 2023

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Population-wide analysis of differences in disease progression patterns in men and women

David Westergaard[1], Pope Moseley[1], Freja Karuna Hemmingsen Sørup[1,2], Pierre Baldi[3] & Søren Brunak[1]

Sex-stratified medicine is a fundamentally important, yet understudied, facet of modern medical care. A data-driven model for how to systematically analyze population-wide, longitudinal differences in hospital admissions between men and women is needed. Here, we demonstrate a systematic analysis of all diseases and disease co-occurrences in the complete Danish population using the ICD-10 and Global Burden of Disease terminologies. Incidence rates of single diagnoses are different for men and women in most cases. The age at first diagnosis is typically lower for men, compared to women. Men and women share many disease co-occurrences. However, many sex-associated incongruities not linked directly to anatomical or genomic differences are also found. Analysis of multi-step trajectories uncover differences in longitudinal patterns, for example concerning injuries and substance abuse, cancer, and osteoporosis. The results point towards the need for an increased focus on sex-stratified medicine to elucidate the origins of the socio-economic and ethological differences.

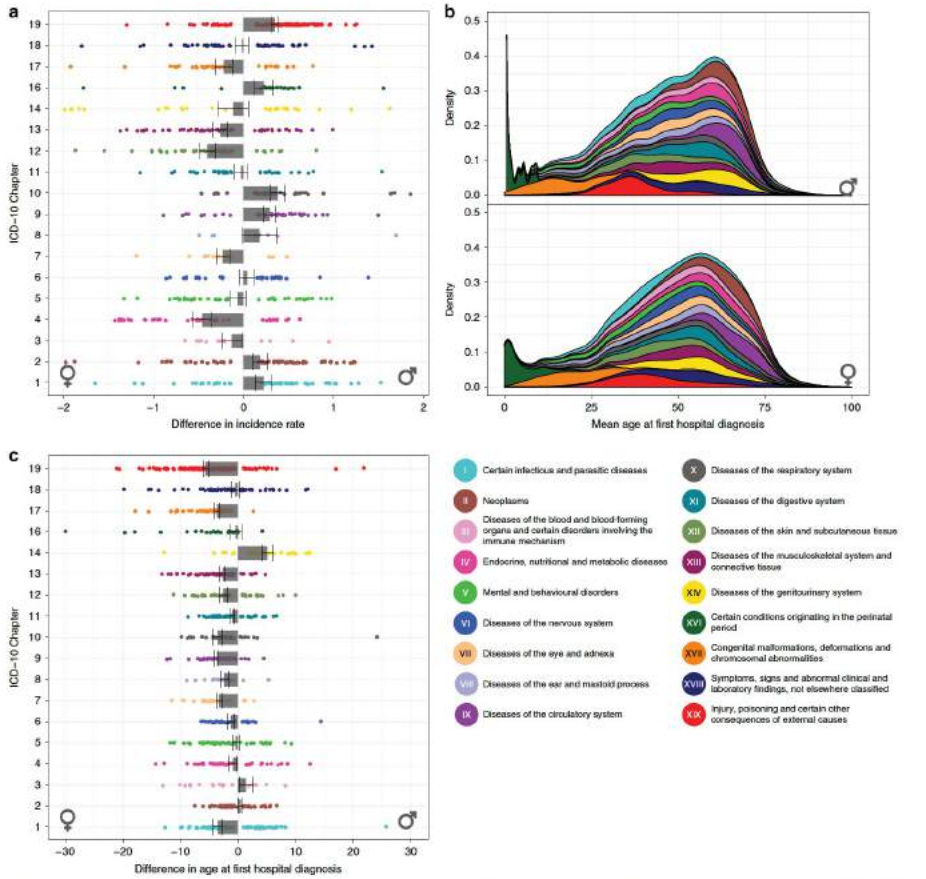
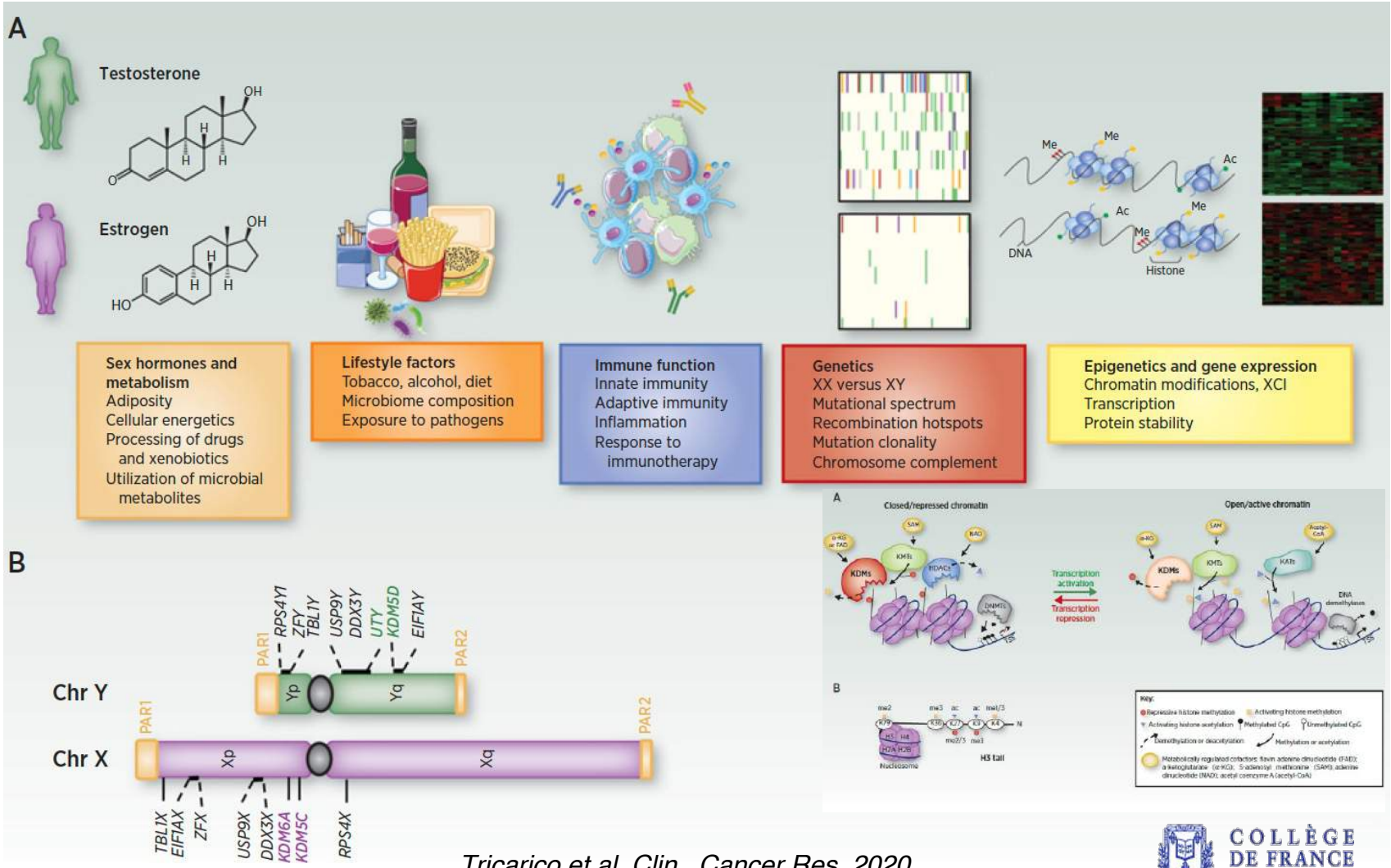


Fig. 1 Incidence and age at first hospital diagnosis of 1369 diagnoses. **a** 344 and 437 diagnoses were found to have a higher age-adjusted incidence rate in men and women, respectively. **b** Mean age at first diagnosis for each of the 1369 diagnoses studied. **c** Mean of the difference in age at first diagnosis. We found 963 diagnoses in which the age at first diagnosis was statistically significant when comparing men and women (Welch's *t* test, FDR < 0.05). Errors bars are the standard error of the mean per ICD-10 chapter

COLLÈGE DE FRANCE 1530

E. Heard, March 6th 2023

Sexual Dimorphism and Human Health



Tricarico et al, Clin.. Cancer Res. 2020

COLLÈGE DE FRANCE 1530

Sex Differences in Biological Aging

Why do women live longer than men?
Are there sex differences in aging-related diseases?

Sex differences in biological aging with a focus on human studies

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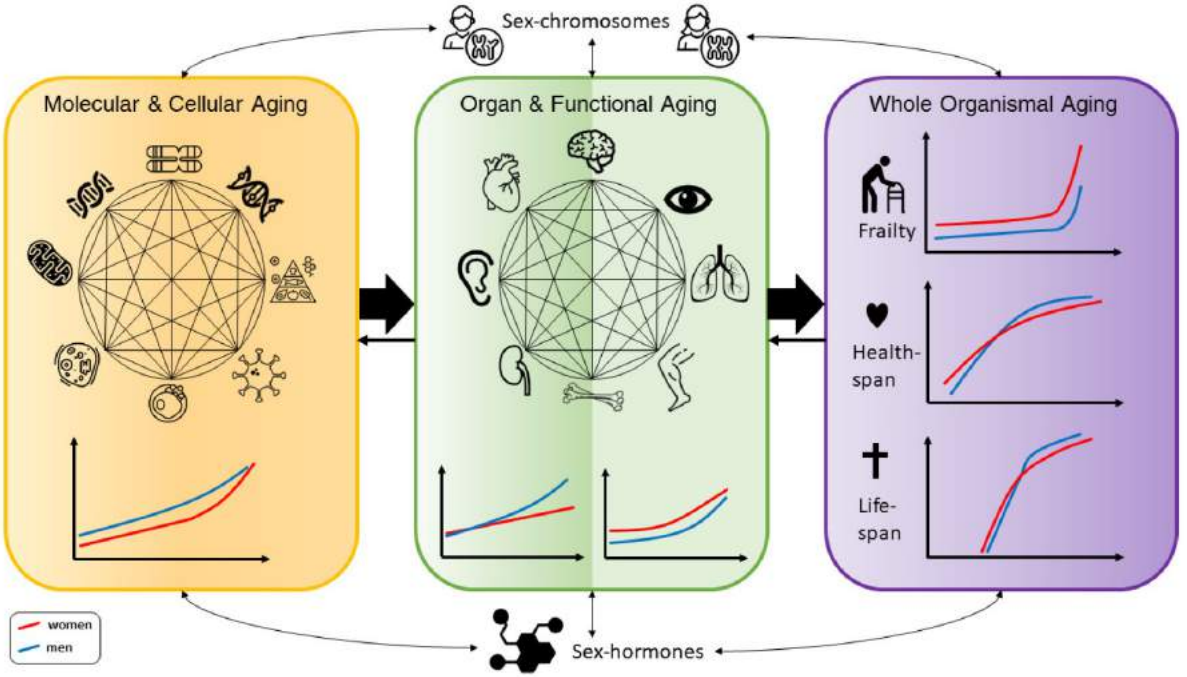
Abstract Aging is a complex biological process characterized by hallmark features accumulating over the life course, shaping the individual's aging trajectory and subsequent disease risks. There is substantial individual variability in the aging process between men and women. In general, women live longer than men, consistent with lower biological ages as assessed by molecular biomarkers, but there is a paradox. Women are frailer and have worse health at the end of life, while men still perform better in physical function examinations. Moreover, many age-related diseases show sex-specific patterns. In this review, we aim to summarize the current knowledge on sexual dimorphism in human studies, with support from animal research, on biological aging and illnesses. We also attempt to place it in the context of the theories of aging, as well as discuss the explanations for the sex differences, for example, the sex-chromosome linked mechanisms and hormonally driven differences.



E. Heard, March 6th 2023

COLLÈGE DE FRANCE 1530

Biological Sex and Gender – Example of Cardiovascular Disease

Cardiovascular disease (CVD) has been and continues to be the leading cause of death in women in most developed countries, with coronary heart disease (CHD) being the main contributor in both sexes

Sex differences in hypertension. Do we need a sex-specific guideline?

Renata Cífková[1,2*] and Larysa Strilchuk[1,3]

Hypertension is the most prevalent cardiovascular disorder and the leading cause of death worldwide in both sexes. The prevalence of hypertension is lower in premenopausal women than in men of the same age, but sharply increases after the menopause, resulting in higher rates in women aged 65 and older. Awareness, treatment, and control of hypertension are better in women. A sex-pooled analysis from 4 community-based cohort studies found increasing cardiovascular risk beginning at lower systolic blood pressure thresholds for women than men. Hormonal changes after the menopause play a substantial role in the pathophysiology of hypertension in postmenopausal women. Female-specific causes of hypertension such as the use of contraceptive agents and assisted reproductive technologies have been identified. Hypertensive disorders in pregnancy are associated with increased risk of maternal, fetal, and neonatal morbidity and mortality, as well as with a greater risk of developing cardiovascular disease later in life. Hypertension-mediated organ damage was found to be more prevalent in women, thus increasing the cardiovascular risk. Sex differences in pharmacokinetics have been observed, but their clinical implications are still a matter of debate. There are currently no sufficient data to support sex-based differences in the efficacy of antihypertensive treatment. Adverse drug reactions are more frequently reported in women. Women are still underrepresented in large clinical trials in hypertension, and not all of them report sex-specific results. Therefore, it is of utmost importance to oblige scientists to include women in clinical trials and to consider sex as a biological variable.

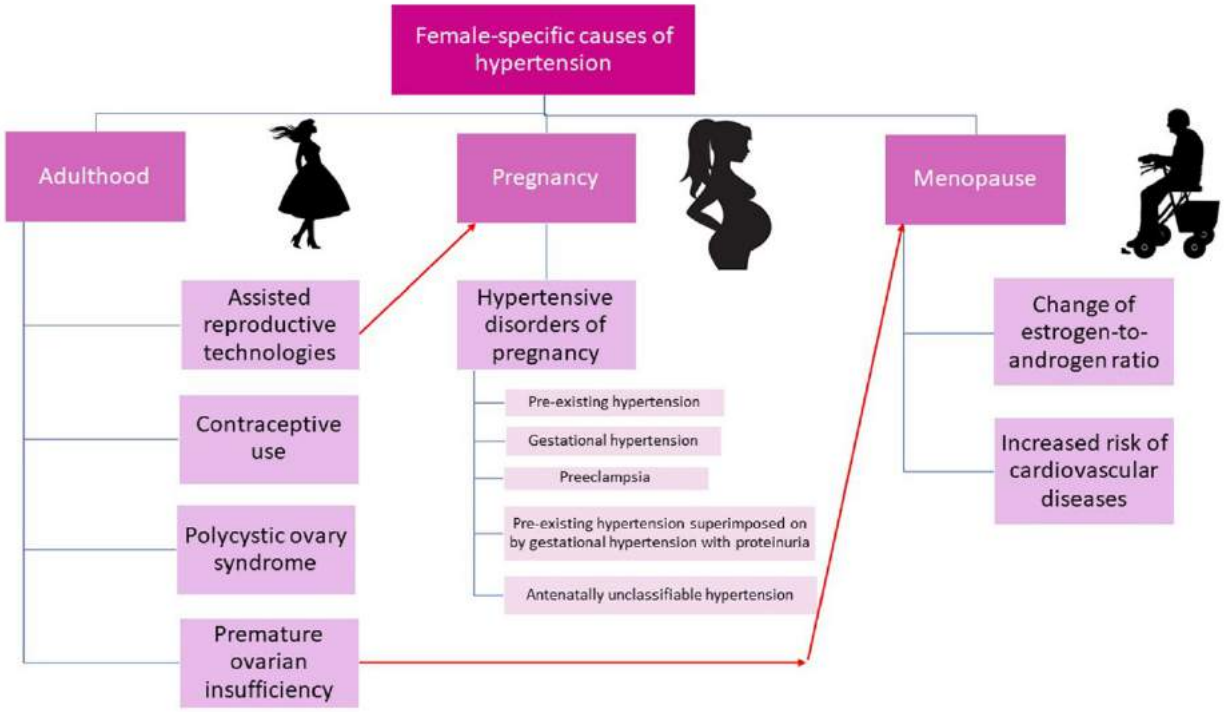


FIGURE 2
Female-specific causes of hypertension.

E. Heard, March 6th 2023

1. Timmis A et al. 2022. European Society of Cardiology: cardiovascular disease statistics 2021. Eur Heart J. 43:716–99. doi: 10.1093/eurheartj/ehab892
2. Yusuf S et al. 2004 Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 364:937–52. doi: 10.1016/S0140-6736(04)17018-9
3. Rapsomaniki E, et al. 2014. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet. 383:1899–911. doi: 10.1016/S0140-6736(14)60685-1
4. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. (2018) 392:1923–94. doi: 10.1016/S0140-6736(18)32225-6

Biological Sex and Gender – Example of Cardiovascular Disease

Despite the growing evidence of importance of gender and biological sex in heart diseases, the distinct contributions of biological sex and the sociocultural dimension of gender to the manifestations and outcomes of ischaemic heart disease and heart failure remain unknown.

Disentangling sex-based differences in genetic and hormonal mechanisms with the complex dimension of gender and its different components and determinants that result in different disease phenotypes is challenging. The relative contribution of purely biological factors, such as genes and hormones, to cardiovascular phenotypes and outcomes is not yet understood.

Increasing awareness of the effects of gender has led to efforts to measure gender in retrospective and prospective clinical studies and the development of gender scores. However, the synergistic or opposing effects of sex and gender on cardiovascular traits and on ischaemic heart disease and heart failure mechanisms have not yet been systematically described.

Furthermore, specific considerations of sex-related and gender-related factors in gender dysphoria or in heart– brain interactions and their association with cardiovascular disease are still lacking

- Sex-related and gender-related factors often have opposite effects on the clinical manifestations and outcomes of cardiovascular disease.
- Some sex-related differences in the human cardiovascular system already exist at birth and are due to purely biological mechanisms, that is, genes and sex hormones.

NEXT WEEK (COURS II) : The Arnold laboratory pioneered the development of mouse models capable of studying differential effects of XX and XY genomes independently of gonadal effects, examined sex differences in the biology of cardiovascular risk factors. The sex chromosome complement affects bodyweight and adiposity, independent of hormones and sometimes in opposition to gonadal sex. These results support the need for study of hormones and sex chromosome genes as separate components of biological sex, as independent targets for future therapies.

Arnold AP, Cassis LA, Eghbali M, Reue K, Sandberg K: Sex hormones and sex chromosomes cause sex differences in the development of cardiovascular diseases. Arterioscler Thromb Vasc Biol 2017, 37:746-756.

Regitz-Zagrosek and Gebhard, Nature Reviews Cardiology, 2022

Sex and gender: modifiers of health, disease, and medicine

Striking sex-based differences in the epidemiology, clinical manifestations, course, and therapy of disease have been acknowledged for years. Although very few of these differences are understood in molecular or cellular terms, the explanations must derive from the fundamental biologic differences between the sexes.

Males and females have different patterns of illness and different life spans, raising questions about the relative roles of biology and environment in these disparities.

Dissimilar exposures, susceptibilities, and responses to initiating agents and differences in energy storage and metabolism result in variable responses to pharmacological agents and the initiation and manifestation of diseases such as obesity, autoimmune disorders, and coronary heart disease, to name a few.

Understanding the bases of these sex-based differences is important to developing new approaches to prevention, diagnosis, and treatment.

Monitor sex differences and similarities for all human diseases that affect both sexes.

Investigators should

- consider sex as a biological variable in all biomedical and health- related research; and
- design studies that will

–control for exposure, susceptibility, metabolism, physiology (cycles), and immune response variables;
–consider how ethical concerns (e.g., risk of fetal injury) constrain study designs and affect outcomes; and
–detect sex differences across the life span.

Sex and gender: modifiers of health, disease, and medicine

What clinicians know about the diagnosis, treatment, and prevention of disease originates from studies mostly done on male cells, male mice, and men.

Historically, for multiple reasons, including the purported safety of women and their offspring, women of childbearing age were excluded from clinical trials. As a result, medical research and care have been centred on male physiology.

The assumption was that male and female cells and animals were biologically identical, and evidence-based medicine was defined by clinical trials done predominantly in men.

In 1993, the US National Institutes of Health (NIH) mandated the inclusion of women in NIH-funded clinical trials, but many investigators did not follow this mandate, and many of those who did include women did not analyse the results by sex, minimising the effectiveness of this policy.

Preclinical research and drug development studies have also predominantly used male animal models and cells. It is not surprising that a 2001 US Government Accountability Office report found that eight of the ten prescription drugs withdrawn from the market between 1997 and 2000 “posed greater health risks for women than for men”. Most funding agencies from Europe and North America have implemented policies to support and mandate researchers to consider sex and gender at all levels of medical research.

Still, the field of sex-based biology and medicine is often viewed as a specialised area of interest, rather than a central consideration in medical research. Essential for the success of clinical care and translational science is awareness by clinicians and researchers that the diseases they are treating and studying are characterised by differences between women and men in epidemiology, pathophysiology, clinical manifestations, psychological effects, disease progression, and response to treatment.

Next Week

13 mars, 2023

Cours II

Biais liés au sexe : comment distinguer les effets dus aux chromosomes sexuels, hormones ou mode de vie ?